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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY

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THE difficulty of positively establishing or definitely excluding the presence of right ventricular hypertrophy by physical or roentgen examination is well known and the need for additional diagnostic procedures is apparent. In spite of the extensive use of the electrocardiogram, there is as yet no general agreement as to its value in the diagnosis of right ventricular hypertrophy. In the first part of this communication the electrocardiographic findings are critically reviewed and elaborated upon. In the second part, an analysis is made of all of our patients in whom the presence of preponderant right ventricular hypertrophy was established at autopsy, and Wilson precordial, Goldberger extremity, and standard limb leads had been obtained during life.

THE CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY FROM THE STANDARD LEADS

An analysis of any large series of patients in whom the presence of preponderant hypertrophy of the right ventricle was established at autopsy has revealed some cases in which the standard leads are normal or exhibit nonspecific abnormalities not suggestive of right ventricular hypertrophy.¹⁻⁴ Thus, the diagnosis may be missed completely if the electrocardiographic study is limited to standard leads.⁵ The question remains as to whether or not there are any

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findings in the standard leads which may be regarded as pathognomonic of right ventricular hypertrophy. Three patterns have been variously considered as more or less diagnostic of right ventricular hypertrophy, namely: (1) definite right axis deviation in the standard leads, which, according to some authors, must be accompanied by RS-T depression and T-wave inversion in Lead III and, according to others, in Lead II, as well; (2) a pattern characterized chiefly by deep S waves in all three standard leads; and (3) certain P wave abnormalities attributable to auricular hypertrophy, which by inference was associated with right ventricular hypertrophy. While right bundle branch block may be associated with right ventricular hypertrophy, it is not diagnostic of the latter, since this conduction defect is most commonly due to coronary disease and may occur even though the right ventricle is normal in weight.^{6,7}

Significance of Definite Right Axis Deviation With or Without RS-T Displacement and T-wave Inversion in Leads II and III.—It has long been known that right axis deviation may result from vertical position of the heart as well as from right ventricular hypertrophy, and much thought has been given to the establishment of criteria which would permit their differentiation. Some authors^{1,5,10} have apparently accepted definite right axis deviation, characterized by an S_1 of greater amplitude than R_1 and by an R_3 of greater height than R_2 , as sufficient evidence for a diagnosis of right ventricular hypertrophy. Others have attempted to express these relationships between the amplitudes of the component parts of the QRS in Leads I and III mathematically, either in terms of the cardiac index¹¹ or in terms of the angle alpha from the Einthoven triangle.¹² The cardiac index, however, is often abnormal in mere vertical position of the heart, and is frequently within normal limits in right ventricular hypertrophy secondary to obstructive emphysema due to the low voltage in the standard leads. Therefore, the cardiac index is more apt to mislead than a casual inspection of the electrocardiogram. Calculation of the angle of the vector, although not subject to the same error as the cardiac index, is no more accurate than an empiric examination of the tracing in differentiating between right axis deviation due to vertical position and that due to right ventricular hypertrophy.¹³ Although an angle exceeding $+110^\circ$ is regarded as abnormal, it is sometimes found in vertical position of the heart without right ventricular hypertrophy, whereas an angle of less than $+110^\circ$ is not uncommon in persons with preponderant hypertrophy of the right ventricle.¹² The fallacy of basing a diagnosis of right ventricular hypertrophy on the presence of definite right axis deviation in the electrocardiogram has been emphasized by Fox and Kremer¹⁴ and will be exemplified and discussed at more length.

Certain continental authors^{15,17} have emphasized the greater diagnostic and more serious prognostic significance of definite right axis deviation when accompanied by an inverted, rather than an upright, T_3 . Von Pein, Papageorgion, and Toelken¹⁸ were unable to confirm this conclusion. Kienle¹⁹ recognized that right axis deviation with negative T_3 may occur in normal vertically placed hearts as well as in right ventricular hypertrophy, but stated that exercise makes T_3 become upright in the former and more deeply inverted in the latter. In

view of the known lability of T_3 , it is unlikely that dependable diagnostic inferences can be drawn from changes in its direction.

Definite right axis deviation, accompanied by RS-T depression and T-wave inversion in Lead II as well as in Lead III, is commonly regarded as diagnostic of right ventricular hypertrophy or "strain," following a concept advanced in 1929 by Barnes and Whitten.²⁰ Although the majority of patients with this pattern have underlying right ventricular dilatation and hypertrophy, it must be emphasized that a substantial minority have no right ventricular lesion whatever. Klainer²¹ has found right axis deviation with inverted T_2 and T_3 in patients where subsequent autopsy revealed isolated left ventricular hypertrophy with or without complicating myocardial infarction. Wilson and associates²² have pointed out that this pattern may occur in uncomplicated left ventricular hypertrophy when the heart is in vertical position. Under these circumstances, the heart is rotated clockwise on its long axis, so that the left ventricle occupies a posterior inferior position, resting upon the diaphragm. The potential variations of the epicardial surface of the posterior wall of the left ventricle are transmitted to the diaphragm and thence to the left leg, resulting in a tall R wave, a depressed RS-T junction, and an inverted T wave in Lead aV_F , which are carried over into standard Leads II and III. The rotation brings the right ventricle more to the left and superior, so that the potential variations of its epicardial surface are referred to the left arm and are registered as a relatively small R and deep S in Lead aV_L , which are carried over into standard Lead I. Goldberger and Schwartz^{23,24} have confirmed this and have further pointed out that definite right axis deviation with RS-T depression and T-wave inversion in Leads II and III may occur in normal subjects when the heart is in vertical position with apex displaced forward. This is exemplified by Fig. 1, which reproduces the electrocardiograms obtained on a young woman with asthenic chest, low diaphragm, and a vertically placed, but otherwise normal, heart. This patient is comparable

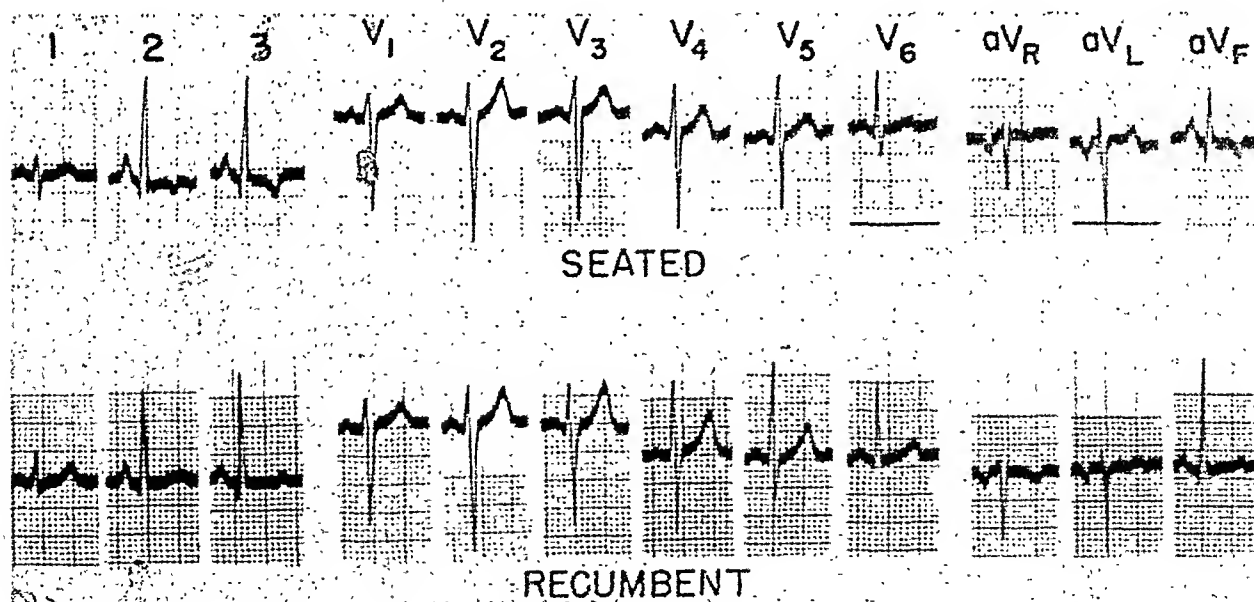


Fig. 1.—Effect of posture on limb leads of a normal person with vertically placed heart.

to those of Goldberger in the occurrence of an inverted T_2 and T_3 , when the diaphragm was further lowered by assumption of the sitting posture and by change to an upright T_2 and diphasic T_3 when the diaphragm rose with recumbency. The negative T_2 and T_3 under such circumstances may be the result of sufficient alteration in cardiac position so that the electrode on the left leg is dominated by potential variations from the posterobasal aspect of the left ventricle near its junction with the left auricle. Tracings obtained through esophageal leads from points opposite the auriculoventricular junction normally reveal a QR complex and inverted T wave, resembling those in Leads aV_F , II, and III of Fig. 1, taken in the sitting position; whereas tracings obtained through more distal esophageal leads opposite the posterior aspect of the left apex normally show the QR complex and upright T wave resembling those in Leads aV_F and II, taken in the recumbent position. The greater amplitude of the P wave in Lead aV_F in the sitting position is in keeping with closer approach of the auricles to the diaphragm and thus lends support to the foregoing hypothesis.

Further evidence that the pattern characterized by definite right axis deviation accompanied by RS-T depression and T-wave inversion in Leads II and III is not pathognomonic of right ventricular hypertrophy, dilatation, or "strain" is afforded by Figs. 2 and 3. In these figures the electrocardiograms of a total of twelve cases are reproduced, arranged in four groups of three cases each. Post-mortem examination established the presence of a normal heart in one patient out of each triplet, right ventricular hypertrophy in another, and isolated left ventricular hypertrophy in the third. From a comparative study of the QRS complexes, the RS-T segments, and T waves of the three cases in each group, it would be difficult or impossible to make a positive differentiation.

It has been implied that predictions can be made not only as to the degree of right ventricular hypertrophy, but also as to the severity and location of the underlying valvular defect from the degree of right axis deviation and the configuration of the T waves in Leads II and III.¹ Since definite right axis deviation with RS-T depression and T-wave inversion in Leads II and III may occur in the absence of right ventricular disease, even greater errors would be expected from diagnostic inferences based upon gradations of the pattern. For the same reason, the statement that right axis deviation in persons with aortic valvulitis indicates the presence of complicating mitral valvular disease¹² is untenable. Furthermore, attempts have been made to interpret certain variations in the pattern as indicative of coexistent left and right ventricular hypertrophy or "strain." Right axis deviation with depressed RS- T_1 and inverted T_1 , left axis deviation with inverted T_2 and T_3 , and a neutral axis with depressed RS- T_1 and RS- T_2 and inverted T_1 have been ascribed to combined left and right ventricular hypertrophy or "strain."²⁵ However, any of these three patterns may be obtained when lesions are confined to the left ventricle, the neutral axis or right axis deviation being due to semivertical or vertical position of the heart and the T-wave abnormalities being traceable to position alone or to complicating myocardial ischemia. It is our intention to elaborate further on this subject in a separate communication on left ventricular hypertrophy.

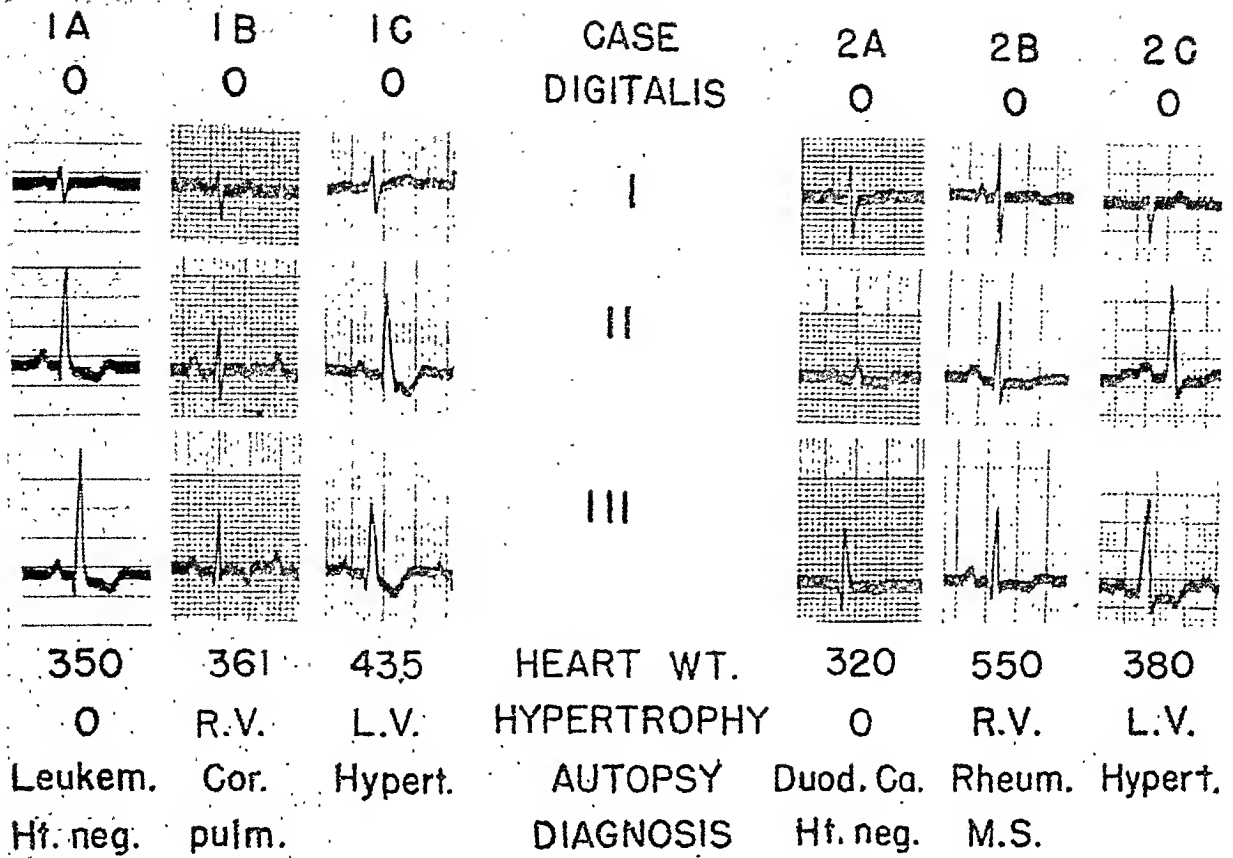


Fig. 2.—Resemblance of right axis deviation due to vertical position to that associated with right ventricular hypertrophy.

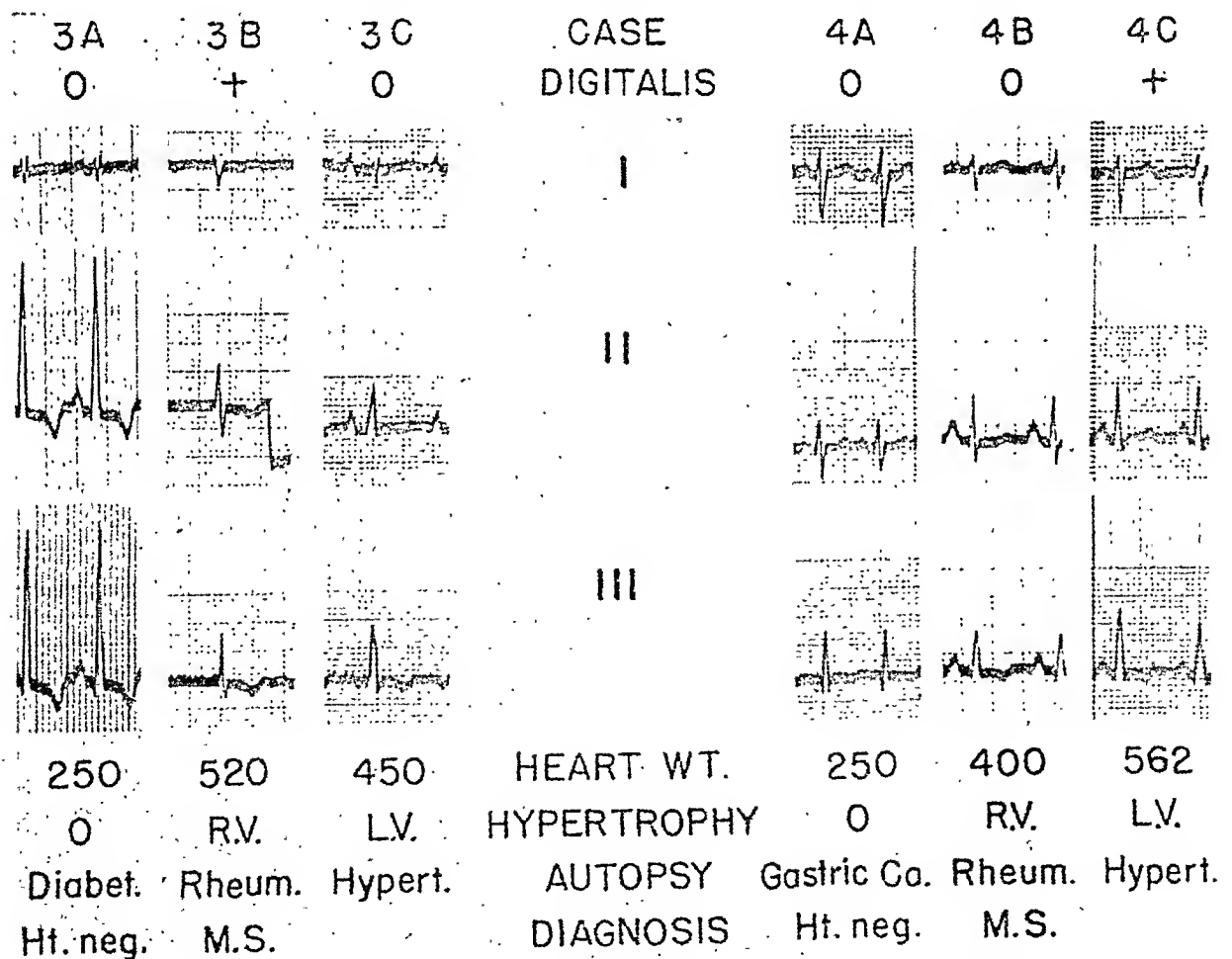


Fig. 3.—Resemblance of right axis deviation due to vertical position to that associated with right ventricular hypertrophy.

A few additional features of the QRS contour in right axis deviation, which have been proposed as aids in differential diagnosis, remain for comment. Goldberger and Schwartz²⁴ have pointed out that a small but definite Q wave is associated with a tall R wave in Leads aV_F , II, and III when right axis deviation is associated with vertical position of the heart, but that no Q wave would be expected in these leads when the tall R is derived from a hypertrophied right ventricle resting on the diaphragm. As mentioned before, the tall R wave found in Leads aV_F , II, and III in vertical position of the heart is derived from activation of the posteroinferior wall of the left ventricle. An interval of 0.01 to 0.02 second normally elapses between the onset of activation of the septum and the arrival of the impulse at the posterior wall of the left ventricle. Negative potentials referred to the left ventricular cavity from septal depolarization are transmitted through the as yet unactivated posterior wall to the diaphragm and thence to the left leg, where they are registered as a Q wave in Lead aV_F and in Leads II and III. With moderate right ventricular hypertrophy, as Goldberger and Schwartz recognized, the heart generally lies in vertical position and QR complexes of left ventricular origin are recorded in Leads aV_F , II, and III. Even with marked right ventricular hypertrophy accompanied by rotation of the heart, so that potential variations of the epicardial surface of the right ventricle are referred to the diaphragm, a QR complex may be found in Leads aV_F , II, and III, similar to that obtained in Lead V_1 .²⁵ A tall R wave, under such circumstances, is due to activation of the hypertrophied inferior wall of the right ventricle and the antecedent Q wave to onset of activation of the septum slightly ahead of the arrival of the impulse in the outer wall of the right ventricle. The undependability of the direction of the initial deflection of the QRS in Leads II and III as a criterion for the differentiation between right axis deviation due to vertical position of the heart and that due to right ventricular hypertrophy is borne out by a study of Figs. 2 and 3. A Q_3 is present in three of the four patients who had right ventricular hypertrophy in these illustrations, absent from one patient having right axis deviation due to left ventricular hypertrophy, and questionable in another.

It has been further pointed out that in vertical position of the heart the QRS of Lead II consists largely of an R wave, whereas in right ventricular hypertrophy it is diphasic, consisting of an RS complex.²⁷ Although this statement holds for the majority of cases, there are a sufficient number of exceptions to make it undependable. For example, a diphasic QRS_2 with prominent S wave was found in two patients (Case 4A of Fig. 3 and in Case A of Fig. 4) both of whom had normal hearts at autopsy. On the other hand, the S wave was insignificant in three patients (Case 2B of Fig. 2, Case 4B of Fig. 3, and in Case B of Fig. 18) all of whom had definite right ventricular hypertrophy at autopsy. Katz and associates²⁸ have amplified the criteria of right ventricular hypertrophy in standard Lead II to include two alternative patterns, namely, the prominent S with upright T, as discussed previously, or a prominent R with inverted T. However, the latter pattern may occur in right axis deviation from vertical position in the absence of right ventricular hypertrophy and even in normal hearts, as exemplified by five patients (Cases 1A, 1C, 2A, 2C, and 3A of Figs. 2 and 3).

Katz and Wachtel²⁹ have stated that a diagnosis of congenital heart disease can be made when two of the standard leads exhibit a high-voltage, diphasic QRS complex whose smaller phase is more than one-quarter the amplitude of the larger phase. Right axis deviation with QRS complexes conforming to this description is most often associated with congenital heart disease, probably because of the tendency to high voltage in such cases and the comparative rarity of high voltage in association with right ventricular hypertrophy due to other causes. However, the foregoing pattern is not pathognomonic of congenital heart disease, because it is very occasionally found in long standing right ventricular hypertrophy from acquired causes and in infants with hearts which are normal to physical and roentgen examination. A gradual tendency for

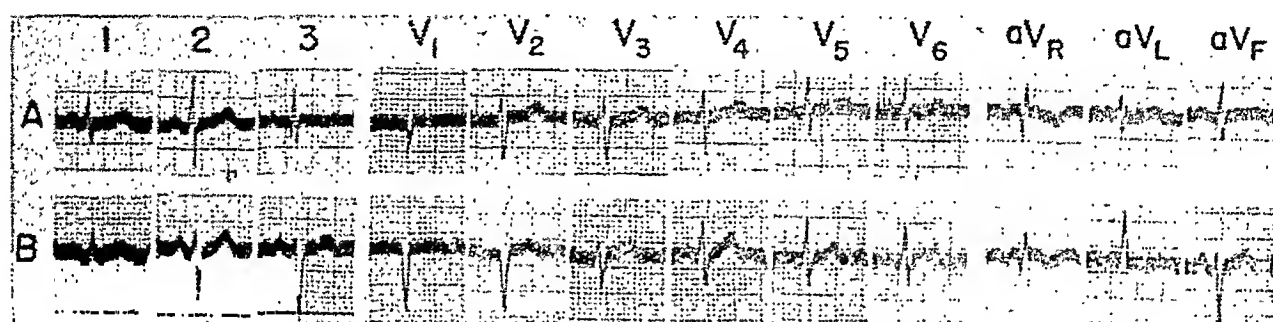


Fig. 4.—Electrocardiograms of two patients proven to have normal hearts at autopsy.

QRS complexes to become more diphasic and to increase in voltage may be observed with gradually increasing right ventricular hypertrophy due to mitral stenosis, as shown in Fig. 5. In acute cor pulmonale, the QRS characteristically becomes diphasic in two or more standard leads and may increase considerably in amplitude, but generally remains within the limits of normal voltage.

Significance of Electrocardiograms Characterized by Predominant S Waves in Each of the Three Standard Leads.—Schwartz and Marcus,³⁰ in a study of 24,200 electrocardiograms, found fifteen records in which the main deflection of the QRS consisted of an S wave in all three standard leads. In each of the nine patients who came to autopsy, right ventricular dilatation and/or hypertrophy was found. The authors also pointed out that the main deflection in each of the three standard leads may be downward as a result of myocardial infarction, but that the downward deflection under these circumstances is a Q wave. They concluded that a predominant S pattern in all three standard leads was due to increased size of the right ventricle, either from hypertrophy or dilatation, or both. Langendorf, Hurwitz, and Katz²⁵ encountered the predominant S pattern in all three standard leads in seven cases and attributed it to coexistent left and right ventricular "strain," obtaining autopsy confirmation in one patient. Goldberger and Schwartz^{24,31} have more recently reinvestigated patients with the predominant S pattern in all three standard leads and have concluded that it may occur in normal subjects, as well as in patients with right ventricular dilatation or hypertrophy. They have attributed the pattern to backward displacement of the apex in a vertically placed heart. Under these circumstances, the

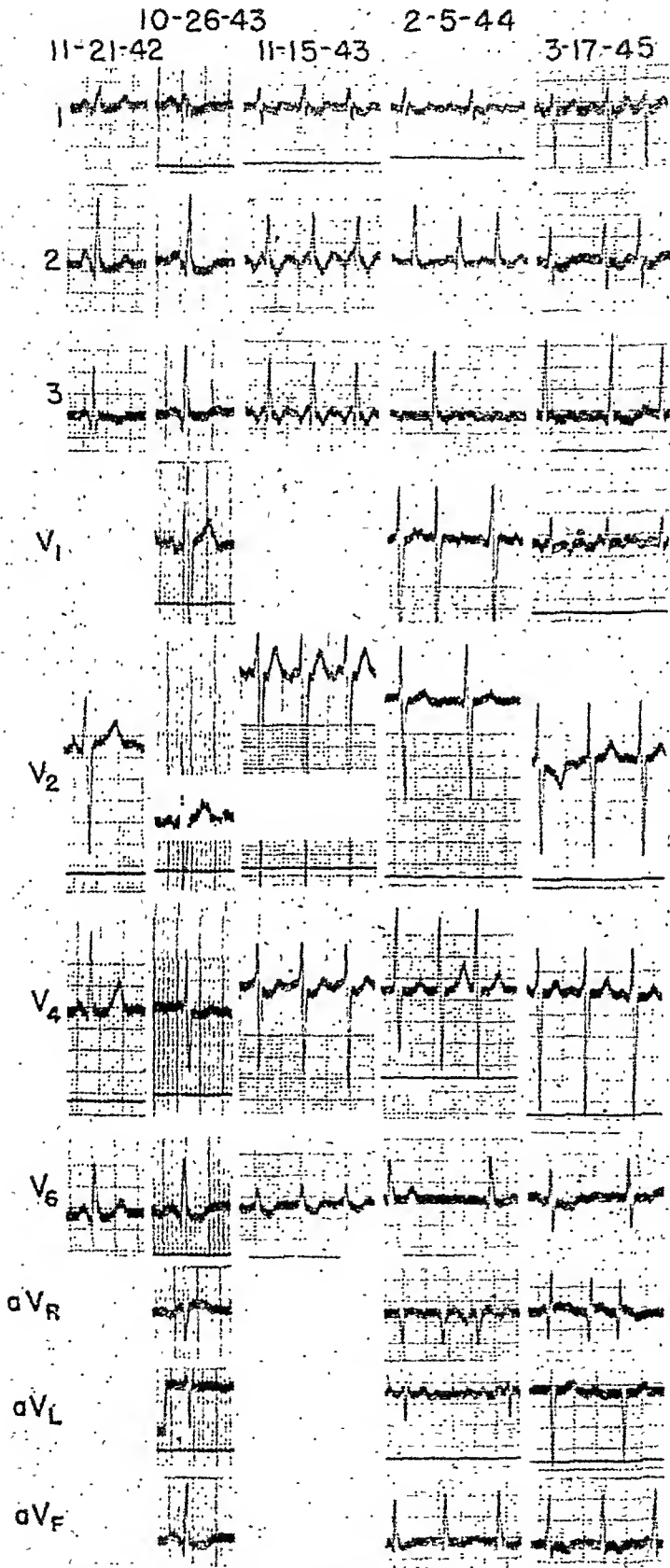


Fig. 5.—Development of electrocardiographic signs of right ventricular hypertrophy in a patient having mitral stenosis.

potential variations of the epicardial surface of the right ventricle are referred to the left leg and are recorded as an RS complex in Lead aV_F and thus contribute to the S wave in Leads II and III. The potential variations of the posterobasal surface of the left ventricle are referred to the right arm and are manifested by a small Q and prominent R wave in Lead aV_R . Since the galvanometric connections to the right arm in standard Leads I and II are the reverse of those in Lead aV_R , the potential variations which give rise to the late upward deflection in Lead aV_R will be recorded as a late downward deflection, or S wave, in standard Leads I and II. This is illustrated in Fig. 9 and will be discussed further in the section on the Goldberger leads. Hence, electrocardiograms characterized by a predominant S wave in all three standard leads may occur with backward displacement of a normal heart and are not diagnostic of right ventricular hypertrophy. Passing mention might be made of an electrocardiogram characterized by a small R and deep S in each of the three standard leads obtained on a patient with situs inversus viscerum,³² the diagnosis being evident from the inverted P and T waves in Lead I. If correction were made for the congenital dextrocardia in that case, the position of the heart would probably be analogous to that of the patient, Case B, in Fig. 4.

Significance of P-wave Abnormalities as Indirect Evidence of the Presence of Right Ventricular Hypertrophy.—Kahn⁸ drew attention to the occurrence of tall, sharply peaked P waves in Leads II and III in bronchial asthma. Winternitz²³ described the pattern under the term "P pulmonale" and attributed it to "strain" on the right auricle secondary to pulmonary disease. Hecht²⁴ stated that the P wave is always altered in right ventricular hypertrophy, and regarded "P pulmonale" as a frequent finding in such cases, but recognized that it may rarely occur in normal hearts. Continental authors,^{35,36} in particular, have regarded "P pulmonale" as evidence of "strain" on the right side of the heart. The problem has been restudied recently by several groups,^{14,24,27,38} who have found the so-called "P pulmonale" in normal hearts in vertical position with forward displacement of the apex and have suggested that its association with pulmonary disease may be a result of alteration in cardiac position from lowering of the diaphragm due to emphysema. The variation in amplitude of the P wave in Leads aV_F , II, and III with change in position of diaphragm is illustrated by Fig. 1. The increased height of the P waves in Leads aV_F , II, and III with lowering of the diaphragm may be due to a change of cardiac position which brings the auricles into closer approximation to the diaphragm, thereby facilitating transmission of their potential variations to the left leg. Hecht²⁴ also described a second pattern characterized by broad, split, and sometimes tall P waves under the term "P mitrale" and contended that it was secondary to mitral disease and never occurred in normal hearts. Although a broad, notched P wave 0.12 second or more in duration may be taken as evidence of an auricular lesion, it can scarcely be accepted as evidence of right ventricular hypertrophy.

CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY
FROM THE PRECORDIAL LEADS

A single precordial lead, particularly the customary Lead IV with exploring electrode at the apex, is of no value whatever either in establishing or excluding the presence of right ventricular hypertrophy. Therefore, no attempt will be made to review reports describing findings obtained with a single precordial lead. Continental authors have made use of two precordial leads. In one of these leads the exploring electrode was applied to the precordium over the left ventricle, and in the other it was applied to the chest wall in the neighborhood of the right ventricle, the latter point varying from the fourth intercostal space at the left sternal border³⁰ to the third rib at the right sternal border.³⁴ Since studies of multiple precordial leads show great variability in the reference point of maximal right ventricular potential variations, a single precordial lead over each ventricle will not serve as an adequate basis for an estimate as to the presence or absence of ventricular hypertrophy. This is exemplified by the study of Langendorf and Katz,⁴⁰ who concluded that chest Leads CF_2 , CF_4 , and CF_5 were of less value in the diagnosis of right ventricular hypertrophy than the standard limb leads.

The necessity of employing multiple precordial leads was early emphasized by Wilson and associates, as a result of their experience with direct leads in animals and in the exposed human heart. They advocated leads from six points on the precordium now accepted as standard reference points. Since the objective of direct epicardial and semidirect precordial leads is to provide an accurate record of the potential variations of the exploring electrode, Wilson minimized the influence of the indifferent electrode through the use of the central terminal. No attempt will be made to review comparative studies of CR, CL, and CF leads because the mere fact that significant differences occur indicates that the potential variations of the remote electrode are sufficiently large to distort the recordings from the precordial electrode.

Wilson and associates^{22,41} have noted a tendency toward reversal in the normal precordial lead relationships in the presence of right ventricular hypertrophy. In leads from the right side of the precordium, they found (1) that the R waves constituted the chief component of the QRS, (2) that a small antecedent Q wave may be present, (3) that S was either absent or relatively small in comparison with R, and (4) that the T wave was characteristically inverted. In leads from the left side of the precordium, R waves were abnormally small, S waves were abnormally large, and T waves were upright. These findings were confirmed by Goldberger.²³

The classical pattern of right ventricular hypertrophy in the precordial leads is illustrated by Fig. 6. The diagnosis is readily made in these cases from a study of the QRS in V_1 , as contrasted with that in V_6 . The diagnostic features in V_1 are the abnormally increased duration and amplitude of the R wave and the absence of an S deflection. The time interval from the beginning of the R wave to the peak is abnormally prolonged, ranging from 0.03 to 0.04 second in the three cases, averaging 0.035 second. The increased duration, together

with the increased amplitude of the ascending limb of the R wave in V_1 , reflects the abnormal thickness of the right ventricular wall. Close scrutiny of Lead V_1 of each of the three cases reveals a small Q wave preceding the R, an abnormal finding in this lead.^{*42} The time interval measured from the onset of ventricular activation (that is, from beginning of Q in V_1) to the arrival of the impulse at the epicardial surface of the right ventricle beneath V_1 (that is, peak of R or onset of intrinsicoid deflection) is even more prolonged, indicating an abnormally late onset and completion of activation of the anterior wall of the right ventricle, a finding characteristic of right ventricular hypertrophy. The abnormally late completion of activation of the right ventricle is confirmed by the absence of S from V_1 , indicating that the anterolateral wall of the right ventricle is one of the last portions of the two ventricles to be completely activated instead of one of the first, as is normally the case.

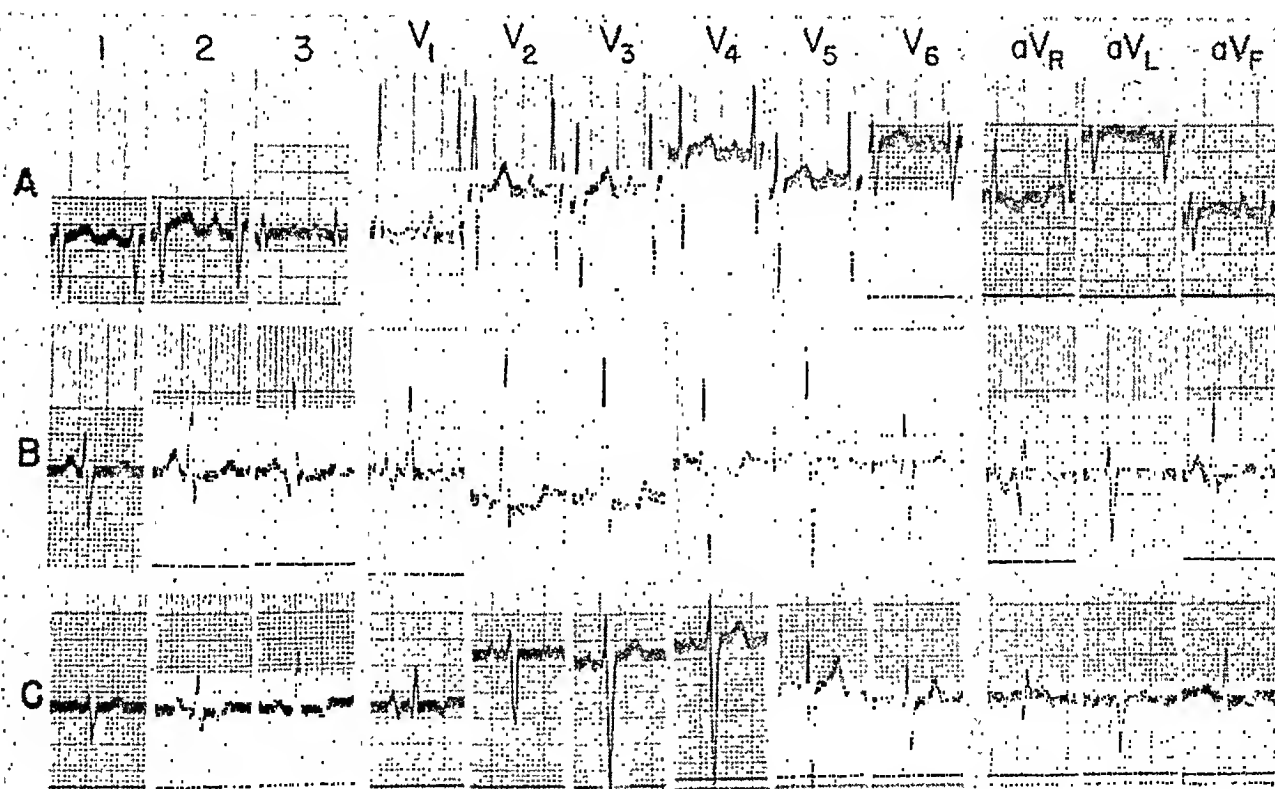


Fig. 6.—Right ventricular hypertrophy.

While attention is being directed to the duration of the individual components of the QRS, it should be noted that the total duration of the QRS ranges from 0.08 to 0.10 second, averaging 0.09 second in the three cases. These measurements are well within normal limits and exclude the presence of complete right bundle branch block. When the R wave in Lead V_1 is abnormally prominent,

*The R wave may be normally absent from V_1 , a QS complex constituting the initial and sole deflection of the QRS under these circumstances. If an R wave is present in V_1 , it should constitute the initial deflection because the impulse normally reaches and begins to activate the anterior wall of the right ventricle very early. An initial Q preceding the R wave of V_1 would suggest a slight delay in onset of activation of this part of the right ventricle, a not uncommon finding in right ventricular dilatation and hypertrophy.

but the total duration of the QRS is below 0.12 second, a careful inspection must be made for double peaking and for abnormal slurring of the R wave in V_1 , resulting from incomplete right bundle branch block, as illustrated in Fig. 10 and discussed later. It will be noted that the R wave in each of the three cases in Fig. 6 shows but one peak and does not exhibit notching or slurring, thus excluding incomplete right bundle branch block in these patients.

The striking contrast between the pattern in V_1 and that in V_6 has already been mentioned as one of the most important features of the electrocardiograms in Fig. 6. The R wave in V_6 is abnormally small in each of the three cases and reaches its peak within the unusually short time interval of 0.02 second. Still more significant, however, is the fact that the R wave in V_6 of each of the three cases is followed by a relatively deep S wave. The attainment of the peak of the R wave in V_6 earlier than in V_1 is the reverse of the normal relationship and indicates that the impulse requires less time to traverse the left than the right ventricular wall in these patients. The continuing activation of the right ventricle results in transmission of negative potentials to the cavity and thence through the completely activated outer wall of the left ventricle to the electrode in Position V_6 , accounting for the S wave.

A progressive decrease in ratio of R to S (or increase in amplitude of S at the expense of R) as the electrode is shifted leftward from Position V_1 to V_6 is typical of right ventricular hypertrophy and is illustrated by one patient (Case A of Fig. 6). The relative amplitude of S in reference to R is greater in V_6 than in any other lead. The fact that the actual amplitude of both the R and S deflections is smaller in V_6 than in V_5 is due to the decrement in potential with increasing distance from the heart. In another patient (Case B of Fig. 6), the close correspondence of the R waves of V_2 and V_3 to that of V_1 and the insignificance of the S waves in all three leads would suggest that the records in these leads are dominated by the potential variations of the epicardial surface of the anterior wall of the right ventricle. The comparable RS relationship in V_4 , V_5 , and V_6 would indicate that the tracings in these leads are dominated by the potential variations of the epicardial surface of the left ventricle. A progressive diminution in the R/S ratio as the electrode is moved from right to left is also demonstrable in the patient (Case B), but not in the patient (Case C). In the latter, the tracings obtained at V_2 and V_3 differ strikingly from that at V_1 , but resemble closely those obtained at V_5 and V_6 . Since the potential variations of the epicardial surface of the left ventricle are largely responsible for the QRS at V_5 and V_6 , they presumably have a dominant effect upon the records obtained at Positions V_2 and V_3 . Thus, the transitional zone between the precordial reference points of the potential variations of the right and left ventricle is further to the right than usual, lying between Positions V_1 and V_2 .

The RS-T junction in Lead V_1 of two patients (Cases A and C of Fig. 6) is practically isoelectric and thus does not reveal the depression sometimes found in this lead in the presence of right ventricular hypertrophy. There is a questionable depression of the RS-T junction in Lead V_1 of one patient (Case B), but a definite depression in right ventricular Leads V_2 and V_3 of this patient. The straight downward slope of the RS-T segment in these leads raises the question

of digitalis action, but the patient had not been receiving this or allied drugs. The convexly upward bowing of the RS-T segment, best illustrated in Case C, and the inversion of the T wave in Lead V_1 of all three cases constitute the usual findings in semidirect leads over a hypertrophied right ventricle, but cannot be attributed to right ventricular hypertrophy unless characteristic changes in the QRS complex are also present. Convexly upward bowing of the RS-T segment and inversion of the T wave may occur normally in Lead V_1 of adults and in Leads V_1 , V_2 , and V_3 of children. Furthermore, sharp inversion of the T wave in Leads V_1 , V_2 , and V_3 may occur in adults as a manifestation of acute cor pulmonale, pericarditis, and anteroseptal infarction or ischemia. These conditions are distinguished from right ventricular hypertrophy by the rapid evolution of the T-wave abnormalities in serial electrocardiograms and by the absence of the abnormalities in the R wave of V_1 and in the R/S ratio in other precordial leads described earlier as characteristic of right ventricular hypertrophy. The upright T wave in Lead V_6 of all three cases is the typical finding in this lead.

Attention has already been drawn to the close resemblance of the tracings obtained at V_1 in each of the three cases in Fig. 6 and the almost identical pattern in V_6 . The patient in Case A was a 15-year-old boy, who had typical clinical and roentgen findings of right ventricular hypertrophy due to patent interauricular septum. The patient in Case B was a young woman, who gave a history of recurrent rheumatic fever and had classical physical signs of mitral stenosis. The patient in Case C was a middle-aged man with chronic cor pulmonale due to pulmonary fibrosis and obstructive emphysema. Thus, right ventricular hypertrophy from different causes tends to give rise to a similar electrocardiographic pattern.

The development of the classical electrocardiographic pattern with gradually increasing right ventricular hypertrophy is illustrated by Fig. 5, which reproduces serial tracings obtained over a period of two and one-half years on a young man with mitral stenosis and gradually increasing right ventricular dilatation and hypertrophy. The early tracings reveal sinus rhythm, subsequently replaced by auricular flutter and then by auricular fibrillation. During the course of the year following the record of Feb. 5, 1944, the S wave disappeared from V_1 and appeared in V_6 , so that the electrocardiogram of March 17, 1945, was diagnostic of right ventricular hypertrophy in the prominence of R in V_1 , and absence of S from this lead, coupled with its relatively great amplitude in leads farther to the left.

The amplitude of the Q, R, and S deflections in V_1 , V_2 , V_5 , V_6 , and aV_R and the time interval from onset of QRS to (1) nadir of Q, (2) peak of R, (3) nadir of S, and (4) end of QRS were measured* in ten additional cases of typical right ventricular hypertrophy. Three of these had tetralogy of Fallot, two had cor pulmonale, and five had mitral stenosis. The minimal, maximal, and average values for each measurement are recorded in Table I. Comparison of the findings in these ten cases with corresponding measurements in normal persons^{43,44}

*At least three representative complexes were measured in each lead according to the method previously described.⁴⁴ The Cambridge measuring device was loaned to us through the kindness of Dr. Frank N. Wilson.

TABLE I. Amplitude of QRS and Deviation of QRS Complex in Leads $V_1, V_2, V_3, V_4, V_5, V_6$ and V_{1-6} [illegible]

reveals the following deviations from the normal: (1) the presence of a Q preceding the R of V_1 or V_{3R} in the majority of the cases; (2) reversal in the ratio of the amplitudes of the R and S waves in V_1 and V_6 , characterized by an abnormally large R in proportion to S in V_1 , a diminution in ratio in leads farther to the left, and a prominent S in V_6 ; and (3) time interval from onset of QRS to peak of R that is abnormally long in V_1 and greater than in V_6 . The findings in V_1 and V_6 need not be as striking as in the cases represented in Table I or in those illustrated in Fig. 6 to suffice for a diagnosis of right ventricular hypertrophy. This will be illustrated and discussed more fully in an analysis of the cases where preponderant hypertrophy of the right ventricle was established at autopsy.

In commenting upon Case C of Fig. 6, it was pointed out that the classical QRS pattern of right ventricular hypertrophy appeared in V_1 , but not in V_2 or V_3 . The diagnosis might have been missed in this case if V_1 had not been obtained, although the similarity of the RS complex in V_2 through V_6 should prompt one to obtain leads from precordial points farther to the right and left. In some cases of right ventricular hypertrophy the diagnostic right ventricular QRS pattern may not appear in either V_1 or V_2 . Goldberger²³ has advocated an additional lead taken from the right upper abdomen with the exploring electrode at the point where the right midclavicular line intersects the lower costal margin. We have not made use of this lead because of the possibility that the potential variations of the posterior inferior surface of the left ventricle might be transmitted through the diaphragm to this region. Wilson and associates have utilized Lead V_E in the diagnosis of right ventricular lesions. We have obtained more help from Lead V_{3R} , in which the exploring electrode is placed on the right chest at a point corresponding to the C_3 position on the left.

The value of Lead V_{3R} in the diagnosis of right ventricular hypertrophy is exemplified by Fig. 7. The relatively small R and deep S in V_6 of Cases A and B aroused the suspicion of right ventricular hypertrophy, but were insufficient for a diagnosis. The pattern in V_1 and V_2 of Case A was suggestive but not diagnostic of right ventricular hypertrophy, whereas that in corresponding leads of Case B was within normal limits. In Case C there was nothing in either the standard leads or in precordial Leads V_1 through V_6 to arouse the suspicion of right ventricular hypertrophy. However, a diagnosis of right ventricular hypertrophy could readily be made from the QRS-T pattern in Lead V_{3R} of all three cases.* The most important feature of Lead V_{3R} is the prominent R wave, which is abnormal in amplitude and duration both in comparison with the S wave of the same lead and with the R wave in leads farther to the left. The sharply inverted T waves associated with the abnormal R in Lead V_{3R} offered further support to the diagnosis. In one patient (Case A of Fig. 7) there were typical physical signs of mitral stenosis, whereas in the patient in Case B there was clinical and roentgen evidence of right ventricular hypertrophy due to chronic pulmonary fibrosis. The patient in Case C came to autopsy, and right ventricular hypertrophy due to chronic pulmonary fibrosis and obstructive emphysema

*Since cases are encountered sufficiently often where an additional exploring lead on the right chest is desirable, we are now taking Lead V_{3R} along with Lead V_1 through V_6 as a routine.

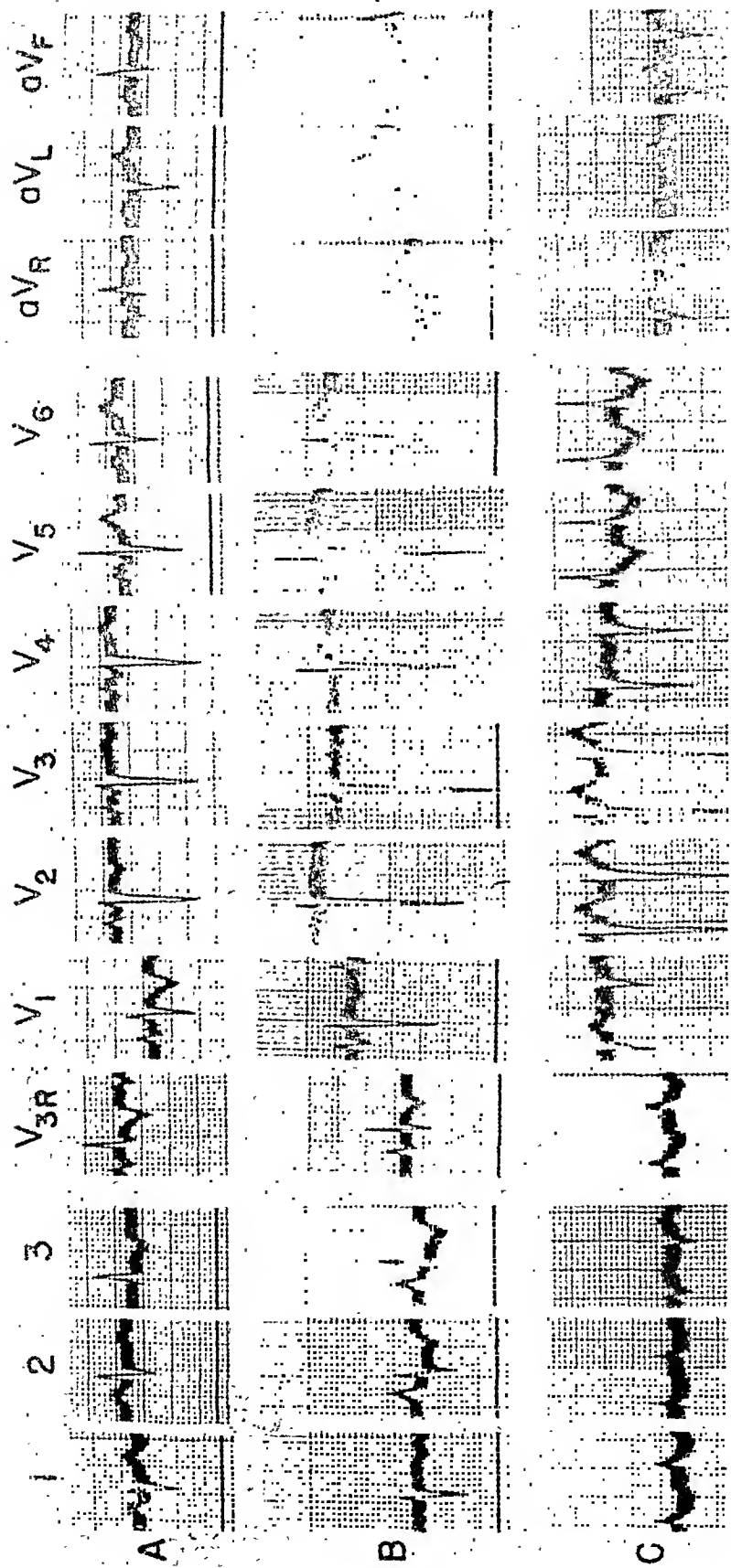


Fig. 7.—The value of Lead V_{1g} in the diagnosis of right ventricular hypertrophy.

was demonstrated. It is entered in Table II as Case 17. Passing mention might be made of the broad, notched P waves in Leads I and II of Case A. These are consistent with the pattern of "P mitrale" and are presumably the result of an auricular lesion secondary to the mitral stenosis. The tall, sharply pointed P waves in Leads II, III, and aV_F of Case B are consistent with the so-called "P pulmonale," but are probably the result of low diaphragms.

In the interpretation of multiple precordial leads, due consideration must be given to the location of the transitional zone between the two ventricles and to the possibility that unusual RS relationships may be the result of alteration in cardiac position with shift in the precordial reference points of the potential variations of the two ventricles. This is illustrated by the cases in Figs 8 and 9.

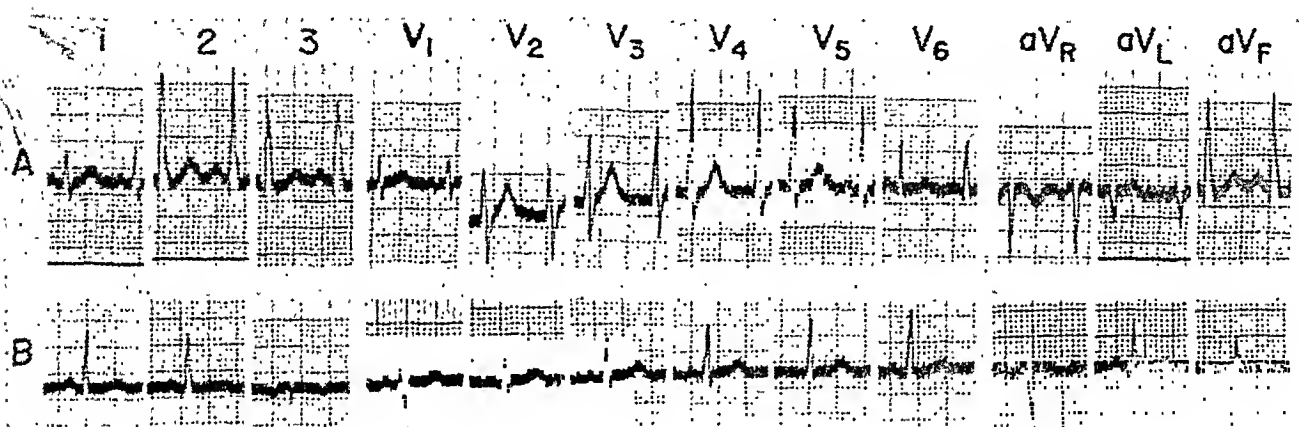


Fig. 8.—Displacement of transitional zone to the right.

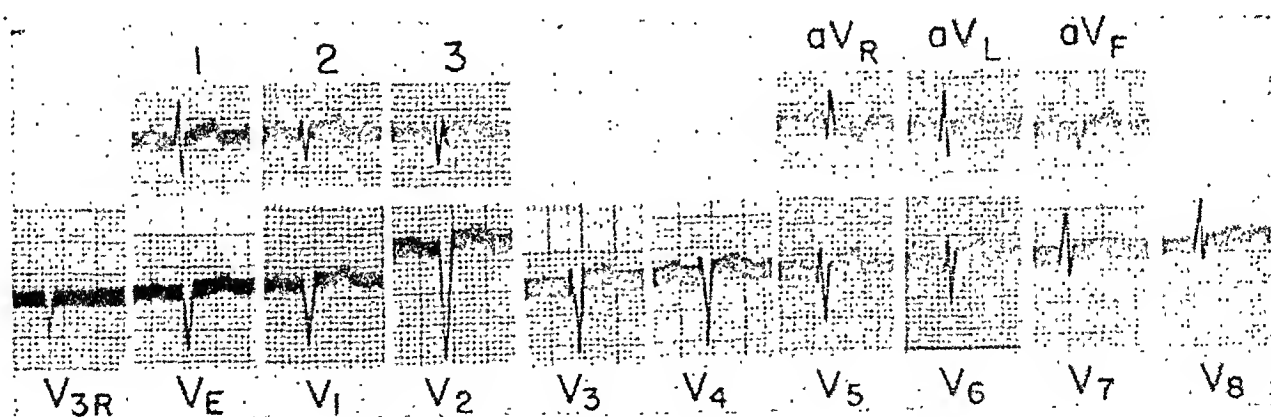


Fig. 9.—Displacement of transitional zone to the left.

A study of Leads V_1 and V_2 of both cases in Fig. 8 reveals that the R wave is relatively tall in comparison with the S. The peak of the R wave is attained slightly later than is customary in these leads under normal conditions. If exclusive consideration were given to these points without due regard to the findings in other precordial leads, an erroneous diagnosis of right ventricular hypertrophy might be made. The fact that the RS-T segments in Leads V_1 and V_2 are normal in contour and that the T waves are upright is, in itself, a strong

TABLE II. ANALYSIS OF ELECTROCARDIOGRAMS FROM PATIENTS

GROUP	CASE NO.	AGE	DIAG.	HEART WEIGHT	LEAD FROM RIGHT PRECORDIUM										
					AMPLITUDE (MM)					TIME (SEC.) FROM ONSET OF QRS TO			RS-T		T
					Q	R	S	R'	RATIO $\frac{R}{S}$	PEAK Q	INT. DEF.	END QRS	JUNC. (MM.)	SEG.	
A	5	45	C. P.	284	1.	6.	1.		0.16	.010	.030	.065	0	X	-2
A	6	67	C. P.	700	2.	2.				.027	.047	.051	0	X	-5
A	7	58	C. P.	382	1.	1.				.020	.050	.065	0	S	+5
A	8	63	C. P.	452	2.	3.				.012	.043	.079	0	X	-1
A	9	45	M. S.	400	1.5	8.				.027	.057	.083	0	X	-5
A	10	64	C. P.	405		10.	2.5		0.25		.027	.058	-1.	V	+1
A	11	52	C. P.	460	0.5	8.	4.		0.5	.008	.035	.078	-2.5	X	-4
A	12	47	M. S.	550		8.	6.		0.75		.020	.076	-1.	V	-1, +1
A	13	56	C. P.	431	0.5	3.5	2.		0.57	.010	.024	.061	0	X	-1
A	14	52	M. S.	439	3.	3.				.013	.033	.067	0	S	-2
A	15	25	M. S.	604		7.					.029	.076	0	X	+5
A	16	22	M. S.			9.					.045	.097	-3.	S	-4
A	43	25	M. S.	440	2.	8.			4.	.018	.064	.080	0	X	-1
B	17	50	C. P.	366	1.	3.				.025	.046	.075	0	X	-2
B	18	51	C. P.	456		0.5	3.5	2.	1.7		.050	.062	0	X	-2
C	19	47	C. P.	584	1.5	1.	2.5		2.5	.020	.038	.079	+1.	S	-5
C	20	42	M. S.	640		3.5	18.				.014	.072	+1.	V	+3
C	21	48	C. P.	420		1.	11.		11.		.008	.064	+5	V	+1
C	22	15	M. S.	592		2.5	6.5		2.6		.015	.082	+5	V	+1
C	23	74	C. P.	305		1.5	14.		9.3		.017	.069	0	S	+5
C	44	37	C. P.	490	5.					.036		.055	0	S	-1
D	24	50	T. F.	486		11.					.073	.093	-1.	X	-1
D	25	55	C. P.	515		0.5	4.	8.	0.5		.058	.098	-1.	S	-1.5
D	26	37	M. S.	487		11.	2.		0.16		.061	.098	-4.	X	-3
D	27	17	C. P.	559		10.	7.5		0.75		.043	.095	0	X	-3
D	28	23	T. F.	460		33.	11.		0.33		.053	.112	0	X	-2, +2
D	29	58	M. S.	550		0.5	3.	3.	1.		.060	.098*	0	X	-5
D	30	38	M. S.	418		1.5	1.5	6.	0.25		.048	.089	+5	X	-1
D	31	44	M. S.	601		0.5	3.	4.	0.7		.060	.085	+1.	X	+1
D	32	55	C. P.	376		3.	7.		2.3		.055	.091	0	V	+1.5
E	33	38	A. A.	575		16.	5.		0.31		.080	.173	-3.	X	-10.
E	34	51	C. P.	387		0.5	2.	14.	0.14		.085	.128	0	V	+1.5
E	35	46	C. P.	440		20.	4.		0.20		.076	.138	0	S	-5
F	36	82	C. P.	323		0.5	9.		18.		.006	.062	0	X	-5
F	37	18	M. S.	324		5.5	23.		4.1		.016	.080	+1.	V	+2
F	38	55	C. P.	400		1.	12.		12.		.013	.094	-5	V	+5
F	39	59	C. P.	416		1.	5.		5.		.008	.050	0	X	-1
F	40	65	C. P.	470		2.	6.		3.		.013	.079	+1.	X	-1
F	41	74	C. P.	613		1.	5.		5.		.010	.072	+5	X	+1
F	42	52	C. P.	460		3.	10.	3.	3.3		.020	.080	0	X	-2

*Measurement in V_2 —Remainder in V_1 .

C.P.—Cor pulmonale

M.S.—Mitral stenosis

T.F.—Tetralogy of Fallot

A.A.—Arteriovenous aneurysm

WITH RIGHT VENTRICULAR HYPERTROPHY PROVED AT AUTOPSY

LEAD FROM LEFT PRECORDIUM										LEAD aV _R							
AMPLITUDE (MM.)				TIME (SEC.) FROM ONSET OF QRS TO			RS-T		T	AMPLITUDE (MM)				DUR. QRS	RS-T		T
Q	R	S	RATIO $\frac{R}{S}$	PEAK Q	INT. DEF.	END QRS	JUNC. (MM.)	SEG.	+, - AMP. (MM.)	Q	R	S	R'		JUNC. (MM.)	SEG	+, - AMP. (MM.)
0.5 1.5	7.	6.	0.85	.005 .010	.015	.063	0	V	+4.	2.	6.			.065	0	X	-2.
	21.	4.	0.19		.031	.081	0	V	+1.	1.	4.			.085	0	X	-.5
	1.	4.5	4.5		.008	.063	0	V	+1.	2.	4.			.062	0	S	-.5
	2.5	6.	2.4		.019	.081	0	V	+1.5	3.	3.			.080	0	X	-.5
	6.	1.	0.15		.030	.087	-.5	X	-2.								
	9.	6.	0.66		.018	.077	0	V	+1.	4.	3.5			.067	0	X	-1.
	3.	14.	4.6		.026	.079	0	V	+4.								
	1.5	4.	5.7		.035	.073	0	V	+2.5	0.5	5.			.056	0	X	-1.5
	1.5	3.	2.		.013	.078	+1.	X	+1.	1.	3.5			.060	0	X	-.5
	8.	8.	1.		.027	.068	-1.	S	-2.	3.	1.			.064	+1.	S	+1.
	4.	10.	2.5		.021	.075	0	V	+2.5	3.	5.			.078	0	X	-2.
	8.	5.	0.62		.026	.095	+.5	X	+1.								
	7.	10.	1.4		.020	.080	0	V	+1.5	5.	3.			.080	0	X	-3.5
1.	9.			.015	.040	.063	0	S	-4.	3.				.050	0	V	+1.5
	4.	S.	2.		.010	.060	0	V	+2.	2.	4.			.061	+1.	X	-1.
1.5	5.	6.	1.2	.019	.027	.064	0	S	+1.		7.			.056	0	S	-.5
	0.5	9.	18.		.008	.077	-.5	V	+.5	0.5	5.5			.072	0	X	-.5
	3.	2.	0.66		.018	.058	0	S	+.5	2.	8.			.067	+1.5	X	-1.
	2.	11.	5.5		.017	.082	+1.	X	-1.	0.5	2.5			.064	0	S	-.5
	2.	5.	2.5		.034	.073	+1.	V	+1.5		3.	1	5	.079	0	X	-2.
	3.	10.	3.3		.015	.060	0	S	-.5		6.			.051	0	X	-.5
0.5	8.5	3.	0.35	.013	.034	.091	0	V	+1.		0.5	5	3	.093	+.5	X	-1.
	9.	7.	0.77		.021	.088	+1.	V	+1.5	6.	6.			.081	0	X	-1.
0.5	8.	13.	1.6	.007	.030	.100	-2.	V	-2.	4.	4.			.088	+1.	X	-1.
	4.	6.	1.5		.022	.103	0	V	+2.	2.	4.			.096	0	X	-1.
	11.	22.	2.		.033	.110	+1.	V	+3.								
	3.	3.	1.		.022	.081	0	V	+1.	2.	5.			.080	+.5	X	-.5
0.5	5.	2.	0.4	.010	.020	.080	0	V	+1.	3.5	2.			.081	0	X	-1.
	1.	9.	9.		.008	.084	-1.	V	+.5	4.	3.			.083	+2.	V	+1.5
	7.	5.	0.71		.035	.085	0	V	+.5	3.	3.			.078	0	V	+.5
	11.	6.	0.54		.032	.180	0	V	+3.	1.5	3.5			.173	0	X	-1.5
	2.	7.	3.5		.018	.128	+1.	V	+2.	1.	4.			.122	0	X	-2.
	6.	2.	0.33		.029	.120	+1.	S	+2.								
1.	16.			.010	.030	.067	-.5	V	+2.	1.	1.			.075	0	X	-1.
	3.	2.	0.66		.030	.077	0	V	+2.	9.	2.			.063	+.5	X	+.5, -.5
	7.	3.	0.42		.013	.074	0	X	-1.5	4.5	4.			.075	+1.	V	+1.5
	8.	4.	0.5		.021	.068	0	X	-1.	4.	4.			.053	0	V	+.5, -.5
	4.				.025	.061	0	V	+.5		0.5	5	1	.061	+.5	X	-.5
	9.	2.	0.22		.023	.061	-2.	S	-2.		1.	4		.058	+1.	X	+2.
	21.	1.	0.04		.041	.085	0	V	+4.	13.	2.			.080	0	X	-3.

RS-T Segment

X—Convex

S—Straight

V—Concave

point against the presence of right ventricular hypertrophy. More important, however, is the observation that the contour of the QRS in V_1 and V_2 of each case is much like that in V_3 , V_4 , V_5 , and V_6 . The S wave gradually diminishes as the electrode is moved from Position V_2 to V_5 and disappears at Position V_6 of both cases. The general resemblance of the tracings in Leads V_1 and V_2 to those from points farther to the left would suggest that the potential variations of the epicardial surface of the left ventricle are playing the dominant role in the recordings from Positions V_1 and V_2 as well as in those from Positions V_3 through V_6 . This may occur with forward displacement of the apex, bringing the left ventricle into closer approximation with the anterior chest wall. Further indirect evidence is afforded by the contour of the P wave in Leads V_1 and V_2 when sinus rhythm is present. The upright P wave with gradually sloping limbs in Leads V_1 and V_2 of Case B represents the typical contour obtained when the exploring electrode is over the ventricle and at a distance from the right atrium. In order to insure adequate coverage of the right ventricle in the multiple precordial leads, it is desirable to have at least one lead to the right of the tricuspid valve. This lead should show either a diphasic P wave containing a sharp intrinsicoid downstroke, indicating that the electrode is over the right atrium, or an inverted P wave, indicating that the electrode is beyond the right border of the heart. In such a lead, and in at least the adjacent lead to the left, the initial upstroke of the QRS should represent a positive potential coming from the right ventricle. Lead V_{3R} was obtained in Case B and was entirely normal for leads over the right ventricle, displaying a diphasic P, a minute R, and deep S. Thus, the tracing at V_1 in this case represents an intermediate complex, the potential variations of the right ventricle being referred to the right of the sternum, and those of the left ventricle, to the entire precordium. The patient in Case A of Fig. 8 died before additional leads could be obtained. Autopsy revealed a normal heart, thereby excluding right ventricular hypertrophy as a cause of the pattern in V_1 and V_2 and lending support to the supposition that the transitional zone was displaced to the right of the sternum.

Fig. 9 is a reproduction of an electrocardiogram obtained in a woman who had no physical or roentgen evidence of a cardiac lesion. If attention is centered on Leads V_5 and V_6 , a small R, a relatively deep S, and an upright T wave will be found similar to the pattern obtained in these leads in cases of right ventricular hypertrophy. However, there was no supportive evidence in Leads V_1 , V_2 , or in supplementary Leads V_E and V_{3R} . The situation is clarified by an examination of Leads V_7 and V_8 , which show a normal left ventricular pattern ordinarily found in Leads V_5 and V_6 . The heart had apparently been rotated so that the apex was displaced backward, the potential variations from the right auricle and ventricle dominating the records obtained from the customary points explored on the anterior chest wall. The transitional zone in this case had been displaced far to the left and posteriorly, the potential variations of the right ventricle having the dominant influence on the recordings in V_5 and V_6 and those of the left ventricle being reflected in V_7 and V_8 . The cases illustrated in Figs. 8 and 9 emphasize the necessity of considering the overall pattern in the interpretation of the precordial leads.

The precordial leads of Cases 24, 25, and 26 depicted in Fig. 10 resemble those of Fig. 6 insofar as the relative amplitude of R and S and the direction of the T waves are concerned. A close inspection of the QRS of Lead V_1 of the first three cases in Fig. 10 reveals a small initial upright deflection, quickly giving way to a downward movement, which reaches the isoelectric line in Case 24 and crosses

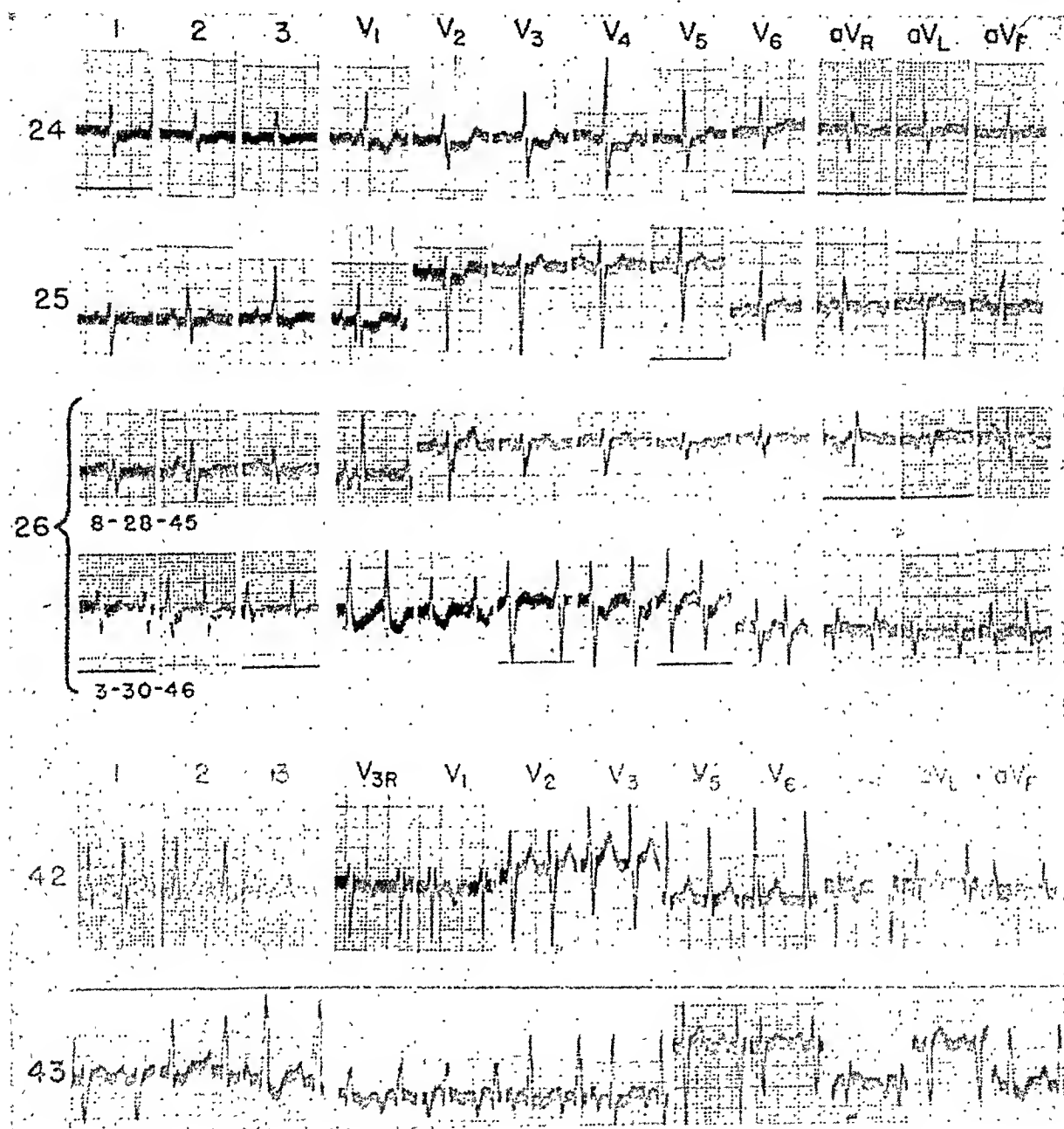


Fig. 10.—Autopsy proved cases of right ventricular hypertrophy exhibiting defective conduction in right ventricle.

it in Cases 25 and 26. This is followed by a very tall R' wave, the peak of which apparently marks the arrival of the impulse at the epicardial surface of the anterior wall of the right ventricle, as judged by the precipitous downstroke, representing the intrinsicoid deflection. The time interval from the onset of the QRS to the peak of the R' wave ranges from 0.058 to 0.073 second, averaging 0.064 second.

The contour resembles right bundle branch block in the double peaking of the R wave of V_1 and in the relatively broad S wave of V_6 . Since the total duration of the QRS is 0.10 second or less in each case, the conduction defect consists in an incomplete rather than a complete right bundle branch block. The initial upward deflection in V_1 is presumably derived from septal activation by impulses passing from left to right, and the R' wave from activation of the outer wall of the right ventricle. The late completion of right ventricular activation, indicated by the late origin of the intrinsicoid deflection in V_1 , is further confirmed by the absence of an S in V_1 in Cases 24 and 26 and by the rudimentary S wave in Case 25.

The patients in Cases 24, 25, and 26 came to autopsy and the presence of preponderant hypertrophy of the right ventricle was established in each. Apart from the right ventricular hypertrophy, no significant myocardial lesion was discovered; therefore, the pattern of incomplete right bundle branch block was attributed to the right ventricular hypertrophy. An incomplete right bundle branch block, however, is not pathognomonic of right ventricular hypertrophy, since it may appear as a transient phenomenon in acute right ventricular dilatation due to pulmonary embolism, in acute myocardial infarction or ischemia, and occasionally in other conditions. The general resemblance of the V_1 pattern of the first three cases in Fig. 10 is noteworthy. Post-mortem examination in one patient (Case 24) showed a typical tetralogy of Fallot. The patient in this case was a 55-year-old woman, who showed no clubbing and had cyanosis only as a terminal event associated with right heart failure. Post-mortem examination in one patient (Case 25) showed chronic cor pulmonale due to obstructive emphysema, and autopsy in the patient in Case 26 revealed a marked mitral stenosis. Thus, the electrocardiographic pattern of incomplete right bundle branch block, associated with right ventricular hypertrophy, is more or less stereotyped, irrespective of the cause of the right ventricular hypertrophy.

Cases 42 and 43 are included in Fig. 10 for contrast purposes. Case 42 deserves special comment because of the presence of an RSR' complex in V_{3R} and V_1 , but not in V_2 . The initial R and S waves were constant, measuring 3 mm. and 10 mm., respectively; but the R' deflection ranged from 0 to 3 mm., the variations apparently being associated with the respiratory cycle. Since the standardization curve showed no overshooting, the R' could not be considered an artefact. The R' deflection in V_{3R} and V_1 was synchronous with the R component of a QR complex in Lead aV_R , as indicated by simultaneous attainment of the peak 0.068 second after the onset of the QRS. In the interpretation of this electrocardiogram prior to death, the late R wave in aV_R was attributed to activation of the posterobasal aspect of the left ventricle and the synchronous R' deflections in V_{3R} and V_1 were thought to be of similar origin. In view of the demonstration of right ventricular hypertrophy at autopsy, it is possible, though unlikely, that the late upright deflections in aV_R , V_{3R} , and V_1 were of right rather than of left ventricular origin and that incomplete right bundle branch block was present. The source of the small late R wave, which is occasionally found in V_{3R} and V_1 after a large downward deflection, needs further elucidation and will be the subject of a future report. A case of a patient having left ventricular hyper-

trophy was recently encountered with a small late R wave in aV_R , V_{3R} , but not in V_1 or V_2 , or in leads over the conus pulmonalis. This late R appeared to be synchronous with the terminal upright deflection in esophageal leads at the auricular level and was recorded in diminishing magnitude along a pathway extending from the midline of the back across the right scapula to the right arm and along a pathway running up the back over the edge of the trapezius and down the anterior chest wall to the V_{3R} position.

The electrocardiogram of Case 43 resembles those of Cases 24, 25, and 26, in the presence of a tall slurred or notched R wave with little or no S in Lead V_1 and in the presence of a prominent slurred S wave in Lead V_6 . However, Case 43 differs significantly from Cases 24, 25, and 26 in the direction of the initial deflection of the QRS in leads from the right side of the precordium. The initial deflection in Leads V_{3R} , V_1 , V_2 , and V_3 of Case 43 is a Q wave, whereas that in Cases 24, 25, and 26 is a small but definite R wave. The Q wave registered in all leads over the right ventricle of Case 43 reflects an initial negativity of the right ventricular cavity and delayed onset of activation of the outer wall of the right ventricle. The initial negativity of the right ventricular cavity excludes right bundle branch block in this case. The notching or slurring of the R wave in V_{3R} , V_1 , V_2 , and V_3 is probably due to a defect in conduction through the hypertrophied outer wall of the right ventricle. The electrocardiographic diagnosis of marked right ventricular hypertrophy in this case was confirmed at autopsy and was secondary to advanced mitral stenosis.

CRITERIA FOR THE DIAGNOSIS OF RIGHT VENTRICULAR HYPERTROPHY FROM THE "UNIPOLAR" LIMB LEADS

The construction of the central terminal enabled Wilson and associates to introduce a new type of limb lead, in which the positive terminal* of the galvanometer was connected to one extremity through the exploring electrode and the negative terminal was connected with all three limbs through the central terminal. Three such leads were taken and labeled in accordance with the point of application of the exploring electrode: V_R when the latter was applied to the right arm; V_L , to the left arm; and V_F , to the left leg. Since the potential variations of the central terminal are generally close to zero and at the most probably do not exceed 0.3 mv., a tracing so obtained will represent largely, but not quite exclusively, the potential variations of the extremity to which the exploring electrode is attached. Hence, limb leads of this type may be regarded as essentially unipolar, in contradistinction to the standard leads which are bipolar in that the potential variations of the two extremities connected to the galvanometer have an approximately equal, but opposite, effect upon the resultant tracing.

Wilson and associates²² noted that the pattern in a given unipolar limb lead was similar to that obtained when the exploring electrode was applied to the trunk at the point of attachment of the respective extremity and often, but not invariably, resembled the pattern obtained in some precordial lead. Wolferth and

*By positive terminal is meant the galvanometric connection which will yield an upright deflection in the electrocardiogram when the potential of the exploring electrode is relatively positive.

associates^{45,46} further investigated transmission of potential variations from precordium to extremities by means of successive records taken as the electrode was moved gradually from an extremity to the precordium and succeeded in demonstrating a pathway along which the QRS-T maintained a fairly constant shape, merely decreasing in voltage with increasing distance from the heart. The pathway leading into the left arm most commonly came from the C_5 position, but sometimes from points higher and more medial. The pathway into the right arm most commonly originated from the C_1 position. The pattern obtained with the exploring electrode on the left leg resembled very closely that registered from any point on the front or back of the trunk below the level of the umbilicus, as well as that obtained when the exploring electrode was placed in the stomach, duodenum, or intestine. This common pattern represented a transmission of potential variations referred from the inferior surface of the heart to the diaphragm and thence to all parts of the body below. Thus, the potential variations of a given extremity are dominated by those of the epicardial surface which faces toward that extremity. This, in turn, is dependent upon the position of the heart in the chest.

A drawback to the Wilson method of recording extremity potentials is the relatively small amplitude of the deflection in some cases. Wilson has overcome this by increasing the sensitivity of the galvanometer, a procedure which is not practical for routine adoption. Goldberger⁴⁷ has introduced a simple modification, which consists essentially in the removal of the connection of the central terminal from the limb to which the exploring electrode is applied. For example, in registering the potential variations of the right arm, the exploring electrode is applied to the right arm and the indifferent electrode to the left arm and left leg. The tracings obtained by the Goldberger procedure are identical in contour with those obtained by the Wilson technique, provided good electrical contact is maintained with each limb,^{47,48} but are 50 per cent greater in voltage. The Goldberger limb leads are thus equivalent to the Wilson limb leads taken with the galvanometer at 1.5 times normal sensitivity. For this reason, Goldberger has referred to his leads as the augmented unipolar limb leads, aV_R , aV_L , and aV_F .

The potential variations of Lead aV_R are dominated by those of the surface of the heart which faces toward the right arm. With the heart in its usual oblique position, the surface which is directed toward the right arm is made up of the atria and great vessels and includes little or none of the epicardial aspect of either ventricle. The portion of the ventricles which faces toward the right arm consists largely, if not exclusively, of valvular orifices, cavities, and endocardium. This is illustrated diagrammatically in Fig. 11,*a* by a lateral view, depicting the surface of the heart visible if one were able to look through the shoulder joint toward the heart after removal of intervening structures and atria. Often the heart is rotated sufficiently on its transverse and anteroposterior axis so that the portion directed toward the right arm includes a small segment of the epicardial surface of the posterobasal aspect of the left ventricle, as in Fig. 11,*b*, or a small segment of the lateral or posterior wall of the right ventricle, as in Fig. 11,*c*.

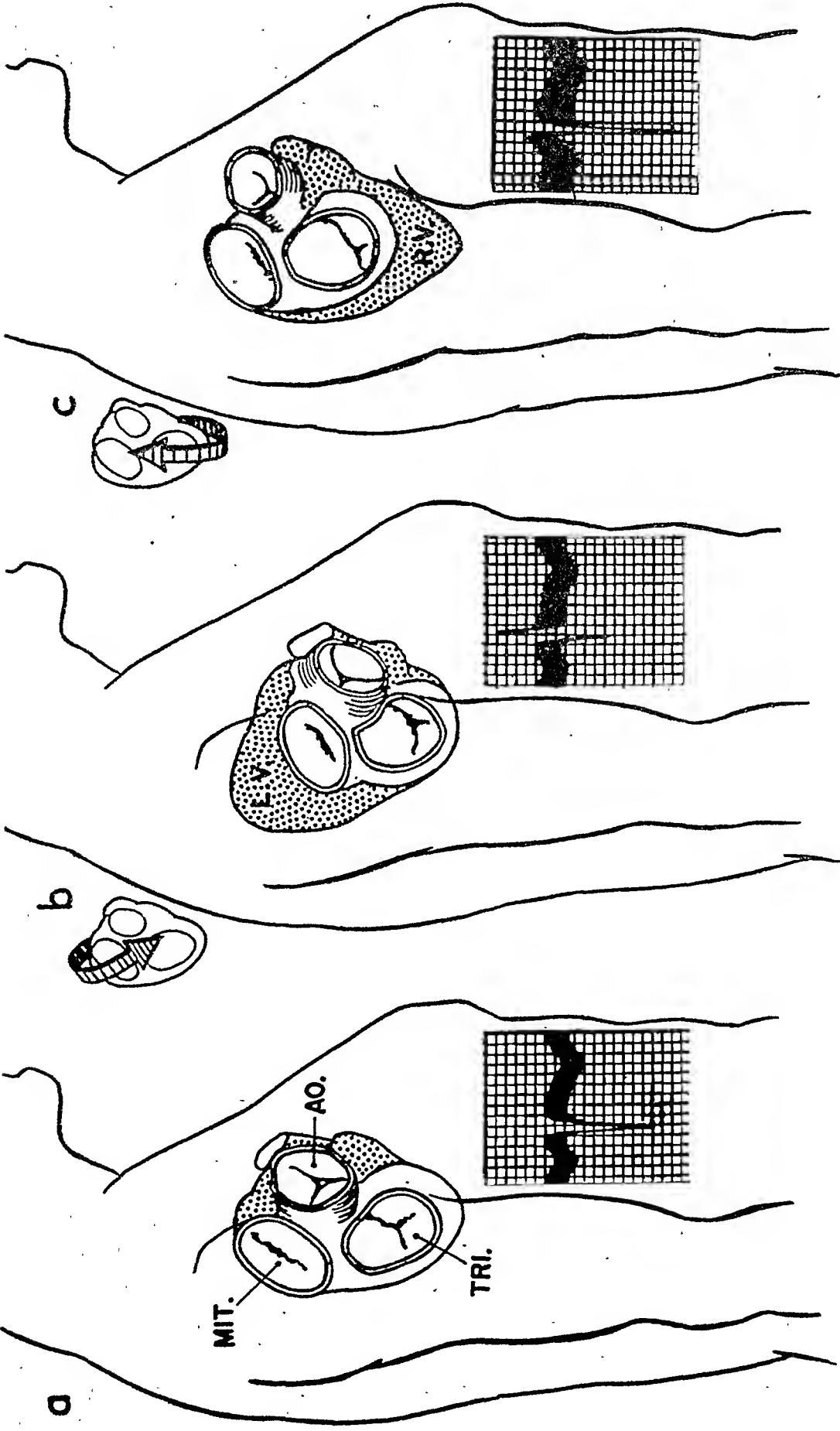


Fig. 11.—Relation between the portion of the ventricles facing toward the right arm and the QRS pattern in Lead aVR.

With the heart in its customary oblique position, the major deflection of ventricular origin in Lead aV_R will be derived from the potential variations of the endocardial surface and cavities of the two ventricles and will thus consist of a downward QRS and inverted T wave. Goldberger^{23,24,31,49,50} has devoted considerable attention to the contour of the QRS in Lead aV_R and has noted that the usual pattern, consisting of a downward major deflection, has four variants, namely: (1) a monophasic QS complex, (2) a minute R followed by a deep S, (3) a deep Q followed by a late R, and (4) a small R and R' separated by a deep S.

The QS complex of Lead aV_R is similar to that obtained by inserting an electrode directly into the left ventricular cavity of dogs.⁵¹ A QS complex is probably obtained in Lead aV_R of man when the heart is so placed that the portion facing toward the right arm consists almost exclusively of the atria and valvular orifices, as illustrated in Fig. 11,*a*.

The RS complex of Lead aV_R is similar to that obtained by inserting an electrode directly into the right ventricular cavity of dogs⁵¹ or human subjects.⁵² The minute initial R wave in aV_R may be due either to earlier onset of activation of the left side of the septum⁵³ or to greater magnitude of electrical forces developed in the left than in the right side of the septum. Either of these alternatives might lead to a momentary positive potential in the right ventricular cavity and thus account for the initial upward deflection in aV_R . Another possible explanation for this small initial R wave might be rotation of the heart so that a portion of the epicardial surface of the right ventricle faces toward the right arm, as illustrated in Fig. 11,*c*, and transmits its initially small positive potentials thereto.

The origin of the QR complex, which occurs as a normal variant in Lead aV_R , is illustrated in Figs. 11,*b* and 12. The heart of the patient shown in Fig. 11,*b* was proven normal at autopsy, whereas that of the patient shown in Fig. 12 was judged normal by physical and roentgen examination. Turning to Fig. 12, the close correspondence of the QR relationships in the esophageal lead at the auricular level to those in Lead aV_R would suggest that the potential variations of the surface of the heart adjacent to the esophagus are transmitted to the right arm. This is borne out by the demonstration of a similar QR complex in leads across the right scapula (that is, at Points *M*, *N*, and *O*) and by the absence of an appreciable R wave in records from the anterior aspect of the right chest, as illustrated by the tracings at Points *J* and *K* over the third rib. The late R wave recorded in esophageal leads opposite the left auricle is probably derived from the adjoining posterobasal surface of the left ventricle, which is the last portion of the heart to become activated. Rotation of the heart, as illustrated in Figs. 11,*b* and 12, brings the posterobasal aspect of the left ventricle into a position facilitating transmission of its potential variations through the back to the right arm, accounting for the QR pattern.

The RSR' complex found in Lead aV_R represents a combination of the second and third patterns discussed.

In right ventricular hypertrophy the heart is often, but by no means always, rotated so that a portion of the outer wall of the right ventricle faces toward the right arm, as illustrated in Fig. 13. The close resemblance of the QRS in Lead

aV_R to that in V_1 of this case suggests that activation of the outer wall of the right ventricle is largely responsible for the R wave in Lead aV_R , as well as that in V_1 . A comparable finding in Lead aV_R was obtained in Case A of Fig. 6, the QRS of this lead corresponding closely to that of V_1 .

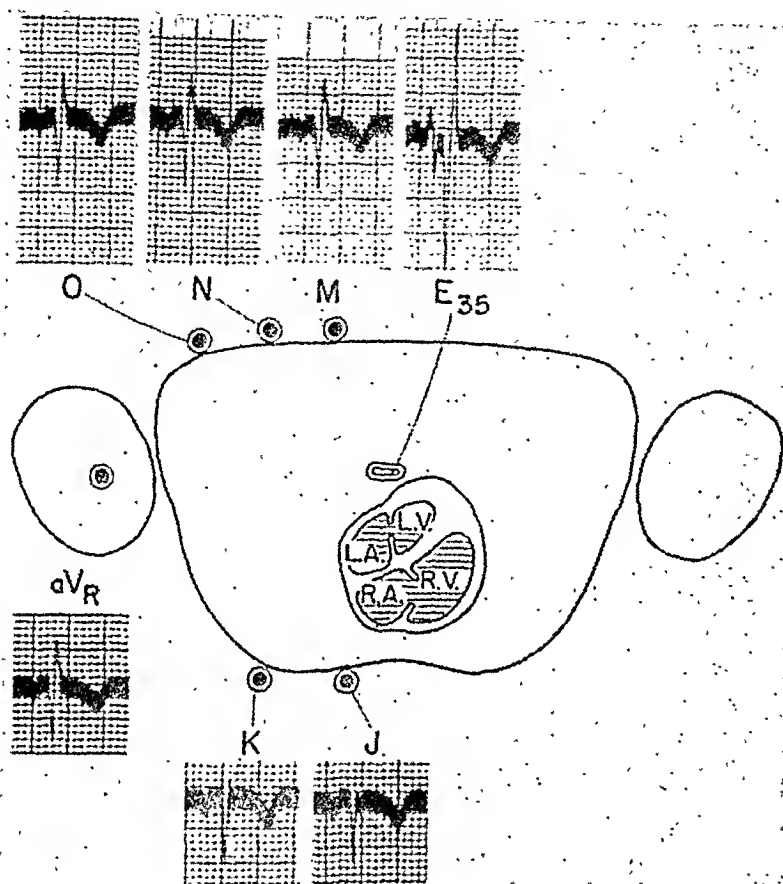


Fig. 12.—Origin of the normal late R wave of Lead aV_R .

The pattern of right ventricular hypertrophy, as registered in Lead aV_R , thus consists of a Q wave larger than that customarily found in Lead V_1 but small in proportion to the succeeding R, characteristically amounting to less than 25 per cent, but in borderline cases ranging from 25 to 50 per cent, of the associated R wave. Lead aV_R is often equivocal or normal when classical signs of right ventricular hypertrophy are demonstrable in Lead V_1 , as exemplified by Cases B and C of Fig. 6. On the other hand, Lead aV_R may exhibit an unusually prominent and definitely abnormal R wave when normal findings are present in V_1 and V_2 . This is illustrated by Case 20 in Fig. 14. This case had signs suggestive of right ventricular hypertrophy in V_5 and V_6 , but not in V_1 or V_2 . The unusually prominent R wave in Lead aV_R , coupled with the findings in V_6 , led to the electrocardiographic diagnosis of right ventricular hypertrophy, which was subsequently confirmed at autopsy.

If a prominent R wave in Lead aV_R could be accepted as *prima facie* evidence of the presence of right ventricular hypertrophy it would make a very helpful criterion. Unfortunately, this is not the case. Goldberger, who has made ex-

tensive studies of the pattern in Lead aV_R , has not stressed the findings in right ventricular hypertrophy, possibly because of his realization that a prominent R wave may appear in this lead from at least two other causes, namely, (1) rotation of a normal or abnormal heart on a transverse axis, so as to carry the apex backward, and (2) in the presence of extensive myocardial damage.

Goldberger & Wilson leads in right ventricular hypertrophy

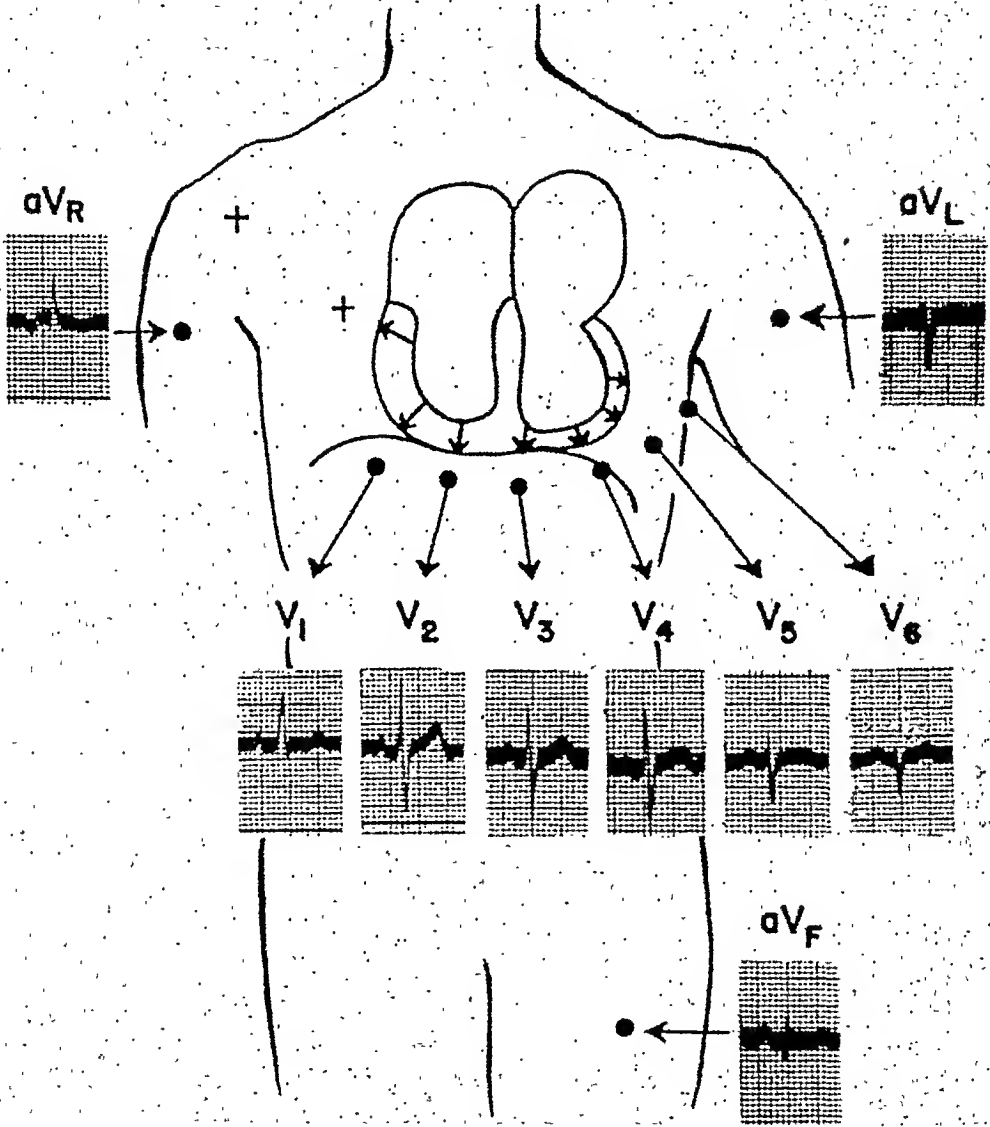


Fig. 13.—Goldberger and Wilson leads in right ventricular hypertrophy.

Rotation of the heart on a transverse axis, so as to carry the apex backward and to the left, will bring the posterobasal aspect of the left ventricle and auricle forward and to the right, as illustrated in Figs. 11,b and 12, and discussed previously. Under these circumstances the contour of the QR in Lead aV_R tends to resemble that in an esophageal lead. The Q wave in esophageal leads is fol-

lowed by a relatively small R if the electrode is above the mitral valve, and by a relatively large R if below the valve opposite the left ventricle. Similarly, the Q wave of aV_R may be followed by a small R if a relatively small segment of the posterobasal aspect of the left ventricle faces toward the right arm, and may be followed by a large R if a considerable portion is directed toward the right arm. This is the probable explanation for the findings in Lead aV_R in the cases illus-

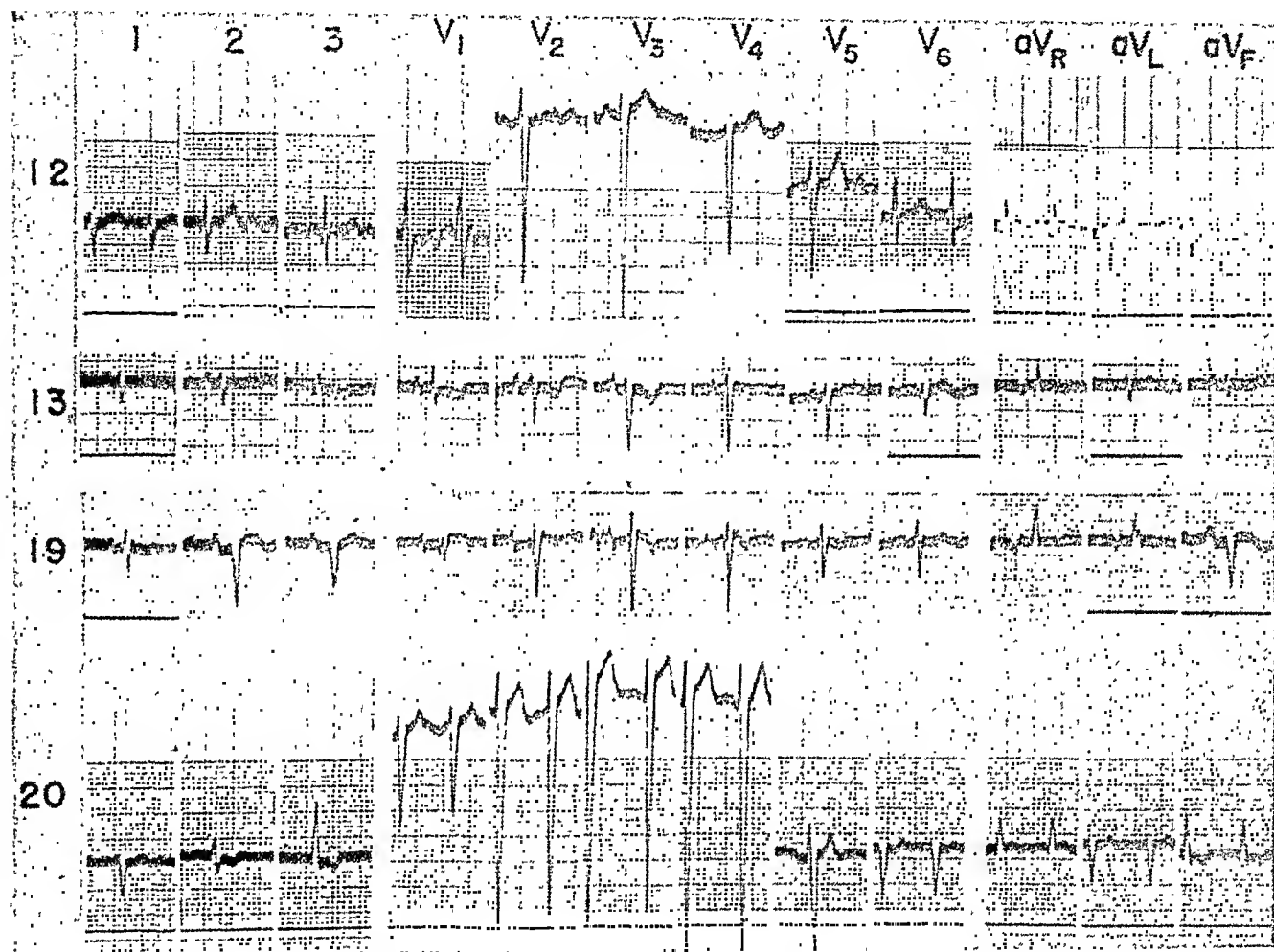


Fig. 14.—Right ventricular hypertrophy confirmed at autopsy.

trated in Fig. 4; both of these patients had normal hearts at autopsy. The variability of these findings is illustrated by Fig. 15, which reproduces two sets of tracings obtained on the same patient on different days. It will be noted that in the first tracing Lead aV_R is represented by a monophasic downward QS complex and in the second tracing by a small Q and a relatively tall R with late peak. The precordial electrocardiogram showed definite signs of left ventricular hypertrophy, which was confirmed subsequently at autopsy. The right ventricle was essentially negative and thus the prominent R wave in Lead aV_R of the second tracing was presumably derived from the posterobasal surface of the left ventricle, as a result of shift in cardiac position. It is noteworthy that in none of the three cases were there signs in the precordial leads suggestive of right ventricular hypertrophy. Thus, a diagnosis of right ventricular hypertrophy cannot be

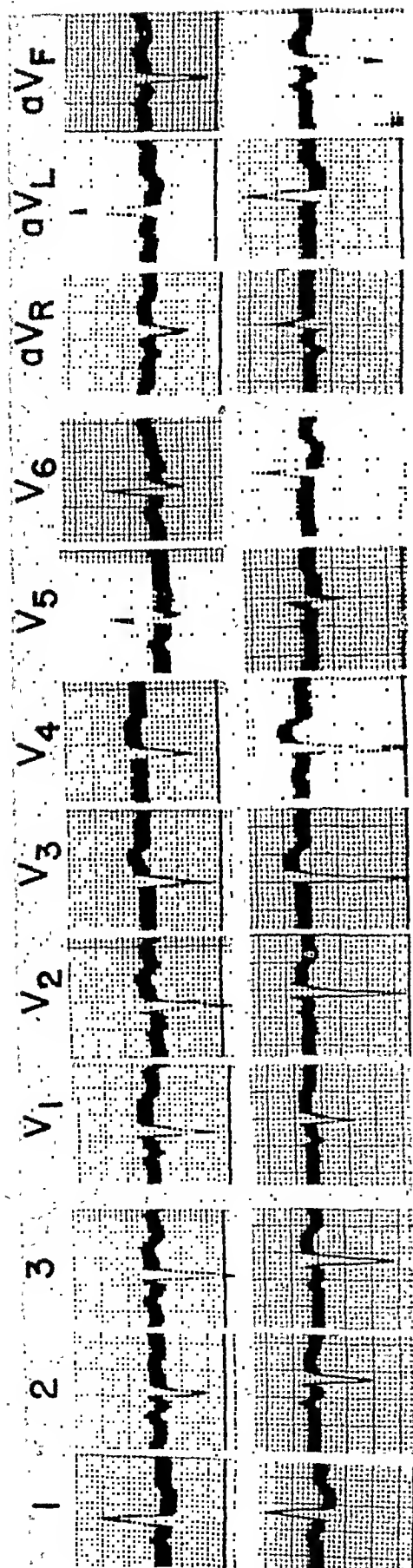


Fig. 15.—Variable R wave in Lead aVR in case of left ventricular hypertrophy.

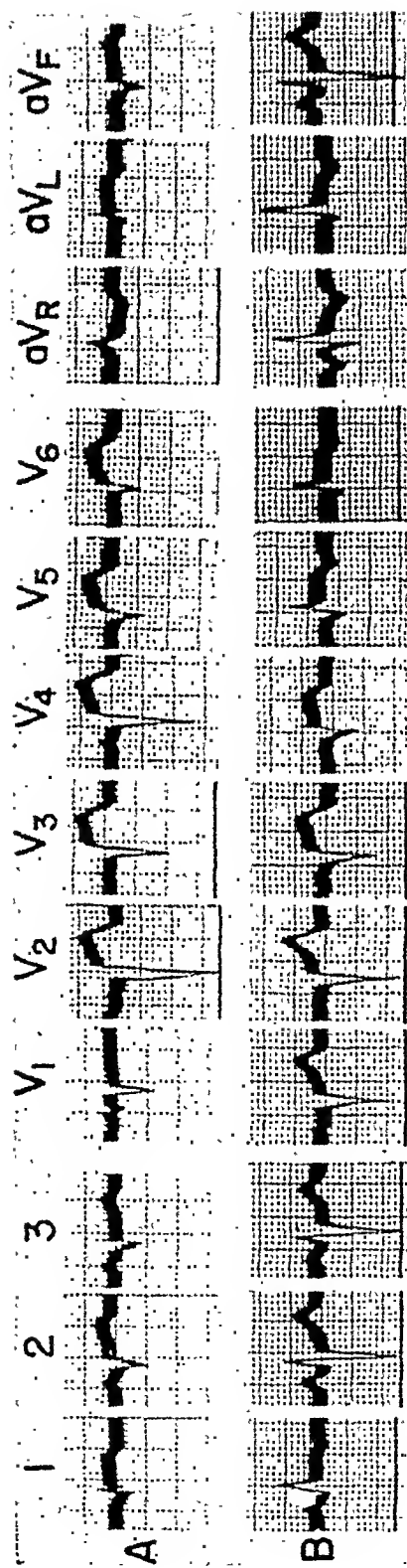


Fig. 16.—Prominent R wave in Lead aVR associated with extensive anterolateral infarction.

based upon findings in Lead aV_R alone, in the absence of supportive findings in the precordial leads.

Goldberger and Schwartz³¹ found that when both the initial and main deflections in Lead aV_R were represented by an upstroke, extensive myocardial damage was invariably present. We have noted such a pattern in Lead aV_R , particularly in cases with extensive anterolateral myocardial infarction. Under these circumstances, the pattern in Lead aV_R may be a reciprocal of that in V_5 , V_6 , or aV_L , as illustrated by Case A of Fig. 16. The diagnosis of extensive infarction of the anterior lateral and posterior walls of the left apex was readily made from the precordial leads and Lead aV_F ,⁵⁴ and was subsequently confirmed at autopsy. The presence of a large anterolateral myocardial infarction may likewise be detected from an inspection of the precordial leads of Case B of Fig. 16 and was subsequently confirmed at autopsy performed on this patient. The QR complex in Lead aV_R of this case resembles more that obtained in esophageal leads from the posterobasal aspect of the left ventricle and may be due to reference of potential variations from this region to the right arm rather than to the infarct itself. A pattern characterized by an R wave as the initial and main deflection in Lead aV_R cannot be accepted as pathognomonic of extensive myocardial damage, since this pattern was present in Case 19 of Fig. 14, where subsequent autopsy revealed preponderant hypertrophy of the right ventricle, but no other myocardial lesion.

ELECTROCARDIOGRAPHIC FINDINGS IN PATIENTS WITH AUTOPSY DIAGNOSIS OF PREPONDERANT HYPERTROPHY OF THE RIGHT VENTRICLE

An analysis has been made of all patients in whom the six Wilson precordial leads were taken during life and a diagnosis of preponderant hypertrophy of the right ventricle established at autopsy. The series comprised a total of forty cases. Lead aV_R was available in thirty-five of the cases and Lead V_{3R} in eight. In thirty-six of the patients, post-mortem study included injection of the heart with radiopaque mass, subsequent roentgenogram, and dissection, as previously described.⁴⁴ The heart was sectioned by the method of Schlesinger⁵⁵ in eighteen of the patients and by the method of Stofer and Hiratzka⁵⁶ in an equal number. The causes of the right ventricular hypertrophy were as follows: cor pulmonale, twenty-four patients; mitral stenosis, thirteen patients, including one with acute right ventricular infarction and one with a stab wound of the right ventricle; tetralogy of Fallot, two patients; and arteriovenous aneurysm, one patient. Hearts with right ventricular hypertrophy, which was secondary to a preponderant hypertrophy of the left ventricle due to such agents as hypertension, were excluded from the series.

The amplitude of the Q, R, S, and R' deflections in V_{3R} , V_1 , V_2 , V_5 , V_6 , and aV_R and the time interval from onset of QRS to (1) nadir of Q, (2) peak of R, (3) nadir of S, (4) peak of R', and (5) end of QRS were measured as previously described.⁴⁴ The results are summarized in Table II. To conserve space, measurements are recorded in three leads, a representative lead from the right precordium (generally V_1 , occasionally V_{3R} or V_2), a lead from the left precordium

(generally V_6 , occasionally V_5), and Lead aV_R . The amplitude of each deflection of the QRS is given in the table, but only the time intervals from onset of QRS to (1) nadir of Q, (2) beginning of intrinsicoid deflection (corresponds to peak of R if a single upright component is present or peak of R' if there are two upright deflections), and (3) end of QRS are included. Notation is also made of the position of the RS-T junction, contour of the RS-T segment, and direction and amplitude of the T wave.

The tabulated cases are classified according to electrocardiographic pattern into the following six groups: (A) Pattern diagnostic of right ventricular hypertrophy in leads from the right precordium (V_1 or V_2), thirteen cases; (B) diagnostic patterns in V_{3R} , but not in V_1 or V_2 , two cases; (C) pattern presumptive of right ventricular hypertrophy in V_6 and aV_R without confirmatory signs in V_1 and V_2 , six cases; (D) incomplete right bundle branch block, nine cases; (E) complete right bundle branch block, three cases; and (F) precordial leads and aV_R not diagnostic of right ventricular hypertrophy, seven cases.

Thirteen cases were classified in Group A because of a pattern in Leads V_1 through V_6 inclusive, which was considered diagnostic of right ventricular hypertrophy on the basis of the following criteria: (1) Reversal in the ratio of the amplitudes of the R and S waves in V_1 and V_6 , characterized by an abnormally large R in proportion to the S in V_1 , a diminution in ratio in leads further to the left, and a prominent S in V_6 . (2) A small Q wave preceded the R wave of V_1 or V_2 in nine of the thirteen patients, indicating slight delay in onset of activation of the outer wall of the right ventricle. (3) Time interval from beginning of QRS to onset of intrinsicoid deflection was abnormally long in V_1 and greater than in V_5 or V_6 . This interval varied from 0.02 to 0.06 second in Lead V_1 and thus usually exceeded, but occasionally overlapped, the normal range of 0.005 to 0.023 second. The electrocardiograms of the two patients from Group A (Numbers 12 and 13), in which this measurement was between 0.02 and 0.025 second, are reproduced in Fig. 14 to demonstrate that the precordial leads as a whole were diagnostic of right ventricular hypertrophy. (4) Total duration of QRS was less than 0.12 second and generally was within normal limits. (5) Notching or double peaking of the R wave of V_1 was absent except in one patient, Case 43 (Fig. 10), where bundle branch block could be excluded and a conduction defect in the outer wall postulated from the presence of a Q wave followed by a notched R in all leads over the right ventricle. Lead aV_R was obtained on ten of thirteen cases in Group A and displayed an abnormal R four times or more the amplitude of the Q wave in two cases and a borderline R two to four times the Q wave in three additional cases. Right axis deviation was present in the standard leads of all thirteen patients and was accompanied by RS-T depression and T inversion in Leads II and III of seven of the patients.

Two cases were classed in Group B because of a diagnostic pattern in V_{3R} , but not in V_1 or V_2 . In one of these, V_{3R} showed definite evidence of incomplete right bundle branch block, whereas V_1 and V_2 were equivocal. The electrocardiogram of the other case (Number 17) is the lowermost of Fig. 7. Lead V_{3R} exhibited a small Q, prominent R with delayed peak, and no subsequent

S wave, whereas V_1 , V_2 , V_5 , V_6 , aV_R , and the standard leads showed nothing to suggest the right ventricular hypertrophy which was found at autopsy.

Six cases were classified in Group C because of presumptive evidence of right ventricular hypertrophy both in leads from the left axilla and in Lead aV_R , but not in V_1 or V_2 . Lead V_{3R} was obtained in one case (Number 23) and was also negative. In each of these patients the S wave was abnormally prominent in leads over the left ventricle and the R was abnormal in aV_R in proportion to the downward deflection in this lead. The R wave constituted the only deflection in Lead aV_R of one of the patients and was from four to ten times the amplitude of the downward component in the remainder. These features are exemplified by Cases 19 and 20, which are reproduced in Fig. 14. A study of Leads V_1 and V_2 reveals no evidence of right ventricular hypertrophy in Case 20, but strongly suggestive, though inconclusive, signs in Case 19. Lead V_{3R} would probably have shown definite signs of right ventricular hypertrophy, at least in Case 19. The standard leads showed right axis deviation in only two of the six cases of Group C. An S wave constituted the chief deflection of each of the three standard leads of two cases. The other two patients had left axis deviation with an RS complex in all three leads, the R wave exceeding the S in Lead I, the S very deep in Leads II and III.

Incomplete right bundle branch block was present in nine patients. The electrocardiograms of Cases 24, 25, and 26 are reproduced in Fig. 10 and have been discussed in detail. One patient (Case 30), who died of a stab wound through the anterior wall of the right ventricle which damaged the septum and who was found to have antecedent right ventricular hypertrophy from mitral stenosis, has been reported elsewhere.⁵⁷ The relative amplitudes of the R and S deflections in the six precordial leads were comparable to those in the electrocardiogram of uncomplicated right ventricular hypertrophy. These cases were differentiated from Group A by (1) notching of the ascending limb of the R wave or double peaking of the upright deflection and absence of Q wave in leads over the right ventricle, (2) a broader S wave in leads from the left side of the precordium, and (3) a longer time interval from onset of QRS to beginning of the intrinsicoid deflection of V_1 or V_2 . This ranged from 0.043 to 0.073 second and thus usually exceeded, but occasionally overlapped, corresponding measurements in uncomplicated right ventricular hypertrophy. Incomplete right bundle branch block was distinguished from complete by a QRS duration below 0.12 second in the former (usually 0.09 to 0.11 second) and 0.12 second or above in the latter. As previously mentioned, incomplete right bundle branch block is not diagnostic of right ventricular hypertrophy since it may occur in acute cor pulmonale, myocardial infarction, and occasionally in other conditions. When due to any of the latter causes, incomplete right bundle branch block is generally transitory; when associated with right ventricular hypertrophy it is usually persistent.

The well-known fact that complete right bundle branch block may be found in right ventricular hypertrophy is borne out by the three cases in Group E. The time interval from onset of QRS to beginning of the intrinsicoid deflection in

leads over the right ventricle exceeded 0.075 second and the total duration of the QRS amounted to 0.12 second or more. However, the finding of complete right bundle branch block does not permit a diagnosis of right ventricular hypertrophy, since the majority of cases with this electrocardiographic pattern in our autopsy series showed primary and predominant left ventricular lesions. In many of the patients the right bundle branch block could be ascribed to infarction of the septum; in some it was thought to be secondary to left ventricular failure. The electrocardiographic and pathologic features will be discussed in more detail in a separate communication.

The seven cases classified in Group *F* represent failures in diagnosis of right ventricular hypertrophy from the electrocardiogram, despite the fact that Leads V_1 through V_6 and aV_R were available in all instances and Lead V_{3R} in two cases. The total heart weight was within normal limits in two of the patients (323 grams and 324 grams, respectively), but the presence of relative right ventricular hypertrophy, as indicated by a ventricular ratio of 1.2,⁶⁶ was the reason for inclusion of these patients. The heart weight in one patient (Case 38) was 400 grams, but the ratio of 1.1 confirmed the presence of right ventricular hypertrophy. The failure of the electrocardiogram to reveal definite signs of right ventricular hypertrophy in this case may have been due to a complicating recent infarction of the subepicardial half of the lateral wall of the left ventricle which was demonstrated at autopsy. The electrocardiogram of one patient (Case 42), showing an inconstant R' deflection in V_{3R} and V_1 , has been reproduced in Fig. 10 and discussed in an earlier section of this communication. The total heart weight was between 400 and 500 grams in two of the remaining electrocardiographic failures and was 613 grams in the last patient. These cases emphasize that a diagnosis of right ventricular hypertrophy cannot be excluded in the absence of signs in multiple precordial and unipolar limb leads.

Within the group of cases of right ventricular hypertrophy, however, there did not appear to be any direct correlation between cardiac weight, ventricular ratio or thickness of the right ventricular wall, and the electrocardiographic pattern. The patient in Case 5 had deep roentgen therapy in 1941 because of a tumor of the right mediastinum. The original electrocardiogram and roentgen study of the heart were negative. During the next five years extensive post-radiation pulmonary fibrosis developed, accompanied by electrocardiographic signs of right ventricular hypertrophy, as illustrated in Fig. 17. Although the total heart weight was only 284 grams, there was definite evidence of right ventricular hypertrophy, as shown by the fact that the thickness of the right ventricular wall and weight of the right ventricular segment equalled that of the left. Thus, the electrocardiogram was diagnostic in this case, but not in the patient in Case 41, in whom the total heart weight and thickness of the right ventricular wall were twice as great. Although there was no direct correlation between QRS pattern and degree of right ventricular hypertrophy, it should be reiterated that the QRS pattern in thirty-three of the forty cases of patients having right ventricular hypertrophy differed specifically from the QRS pattern in patients with normal hearts at autopsy.⁴⁴

Two of the seven patients whose precordial and unipolar extremity leads failed to show signs of right ventricular hypertrophy had right axis deviation in the standard limb leads with depressed RS-T₂ and RS-T₃ and inverted T₂ and T₃. However, this pattern may occur in left ventricular hypertrophy and even in normal subjects when the heart is in vertical position, whereas the changes in the precordial leads displayed by Groups A and B are diagnostic of right ventricular hypertrophy. The confusion which may arise from the standard leads and the

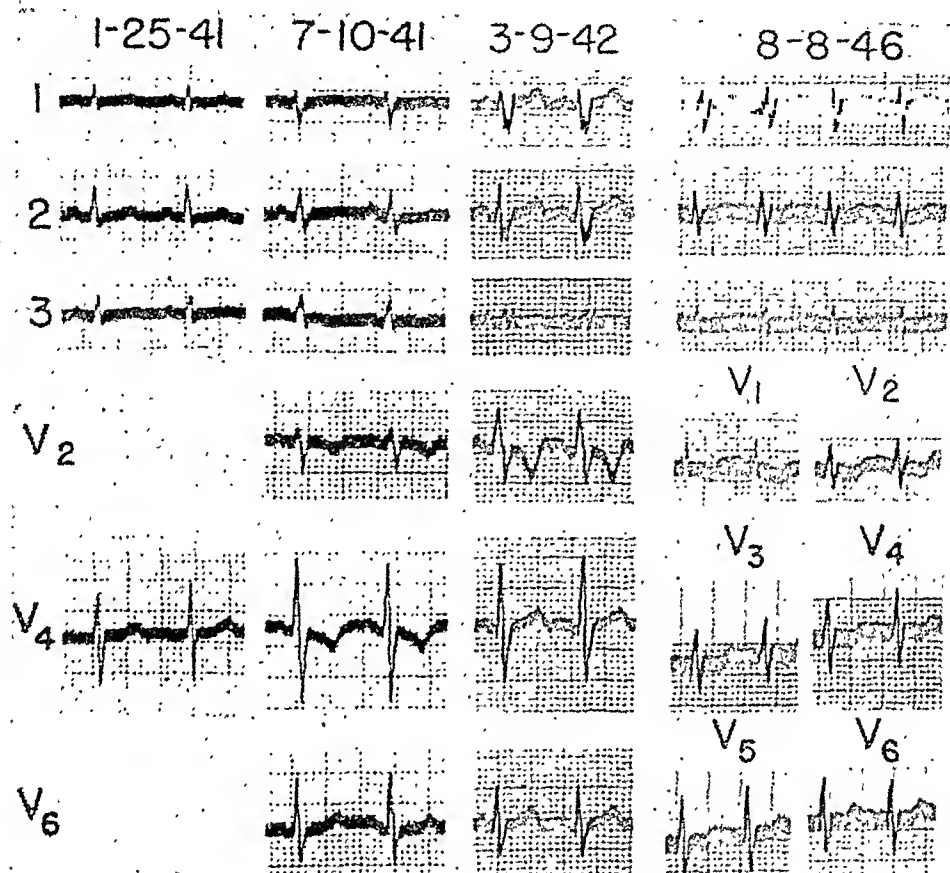


Fig. 17.—Development of electrocardiographic signs of right ventricular hypertrophy.

clarification afforded by the multiple precordial leads is illustrated in Fig. 18. The standard leads of the four cases were closely comparable and Lead III was almost identical. The differentiation of Cases A and B from Cases C and D would be difficult or impossible from the standard leads alone, but is easy from the multiple precordial leads. In Cases A and B, the R wave of Lead V₁, though small in amplitude, is highly significant because of the late peak and absence of S which, together with the diminishing R/S ratio in leads further to the left and the deep S in V₆, permits a definite diagnosis of right ventricular hypertrophy. Chronic cor pulmonale was demonstrated at autopsy in two patients (Cases A and B, which are listed in Table II as Cases 7 and 8, respectively). The pattern in V₁ and V₆ in Cases C and D contrasts sharply with that in Cases A and B and strongly suggests the presence of left ventricular hypertrophy. Isolated left ventricular hypertrophy, of hypertensive origin was found at autopsy in two

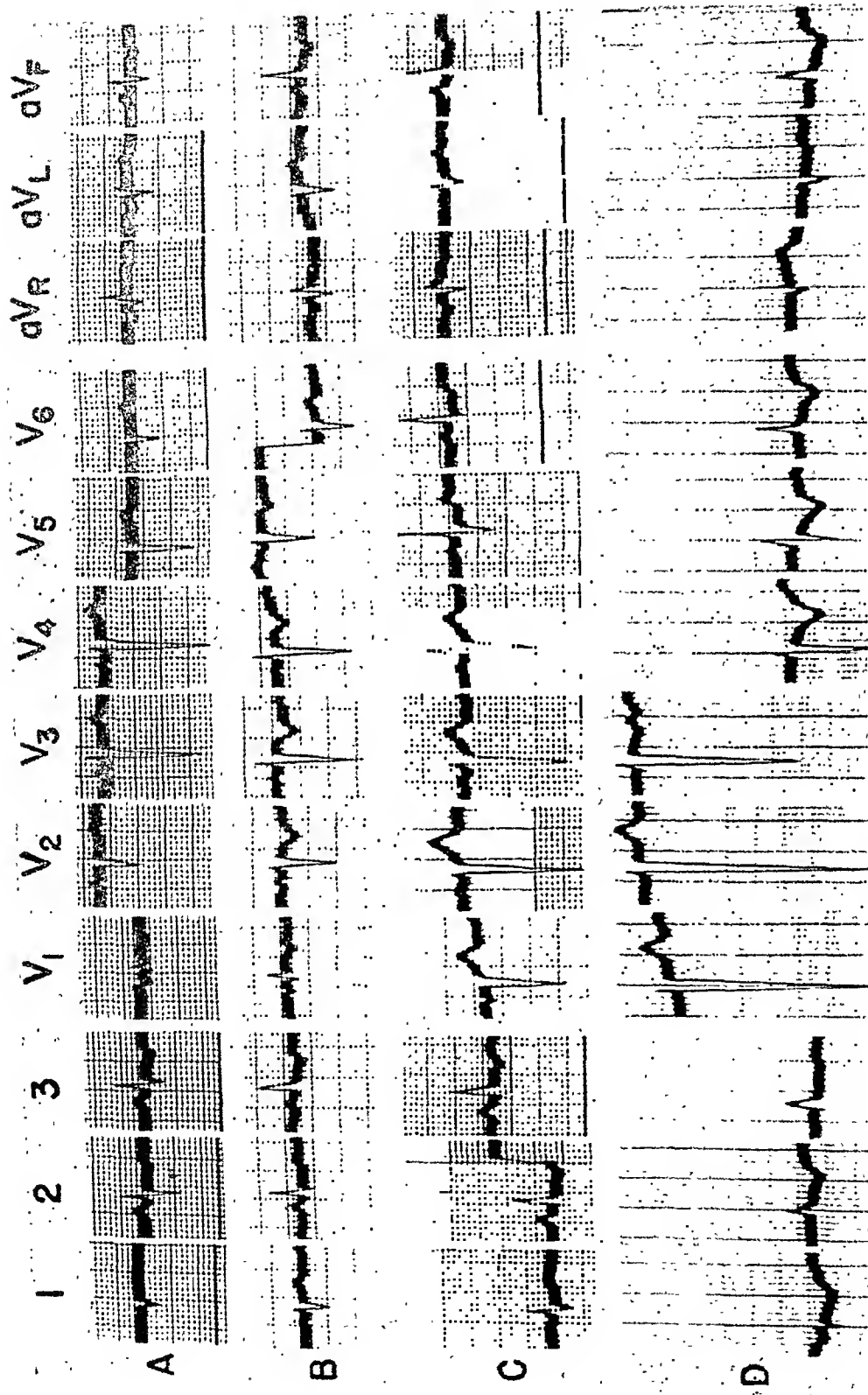


Fig. 18.—Two cases of autopsy-proven right ventricular hypertrophy (A and B) contrasted with two cases of autopsy-proven left ventricular hypertrophy (C and D).

patients (Cases C and D). In Case C autopsy also disclosed an organizing infarct confined to the subendocardial layer of the basilar half of the posteroseptal wall of the left ventricle. This infarct was completely missed in the ante-mortem interpretation, and was probably not responsible for the electrocardiographic pattern since tracings taken on a former admission, before the advent of the infarct, were similar to that in the illustration. This Case will be discussed in more detail in a subsequent paper on posterior infarction.

SUMMARY

1. The electrocardiographic criteria for the diagnosis of right ventricular hypertrophy have been evaluated and elaborated upon through a critical review of the literature and a study of our clinical and autopsy material.

A detailed description is given of the findings in the standard limb leads, the Wilson precordial leads, and the Goldberger unipolar extremity leads.

2. An analysis is presented of all of our cases of patients in whom Leads V_1 through V_6 , inclusive, and the standard limb leads were obtained during life and a diagnosis of preponderant hypertrophy of the right ventricle was established at autopsy. The series comprised a total of forty cases. The augmented unipolar limb leads were available in thirty-five of the cases and Lead V_{3R} in eight. The amplitude of each deflection of the QRS in V_{3R} , V_1 , V_2 , V_5 , V_6 and aV_R was measured and the time interval from the onset of QRS to (1) the nadir of Q, (2) peak of R, (3) nadir of S, (4) peak of R' , and (5) end of QRS was determined in each of these leads with the aid of a Cambridge measuring device. In thirty-six of the patients post-mortem study included injection of the heart with a radiopaque mass, subsequent roentgenogram, and careful dissection.

3. The forty cases of patients proven to have preponderant right ventricular hypertrophy at autopsy were classified according to electrocardiographic pattern into the following six groups:

(A) Pattern in Leads V_1 through V_6 , inclusive, was considered diagnostic of right ventricular hypertrophy in thirteen cases on the basis of the following criteria: (1) reversal in the ratio of the amplitudes of the R and S waves in V_1 and V_6 characterized by an abnormally large R in proportion to S in V_1 , a diminution in ratio in leads further to the left, and a prominent S in V_6 ; (2) time interval from beginning of QRS to onset of intrinsicoid deflection that was abnormally long in V_1 (generally between 0.03 and 0.05 second) and greater than in V_5 or V_6 ; (3) tendency to a small Q wave in V_1 ; (4) tendency to inversion of the T wave in V_1 and to upright T wave in V_6 ; (5) total duration of QRS less than 0.12 second and generally within the normal range; (6) absence of notching or double peaking of the R wave of V_1 , except in one case where bundle branch block could be excluded and a conduction defect in the outer wall of the right ventricle postulated from the presence of a Q wave followed by a notched R in all leads from the right side of the precordium. The electrocardiographic findings were similar, irrespective of the cause of the right ventricular hypertrophy.

(B) Pattern typical of right ventricular hypertrophy was present in Lead V_{3R} , but not in V_1 or V_2 in one patient, and signs of incomplete right bundle branch block were distinctive in V_{3R} , but not in V_1 or V_2 of another patient.

(C) Pattern presumptive of right ventricular hypertrophy was present in Lead V_6 and aV_R in six patients without confirmatory signs in V_1 or V_2 . This pattern consisted of an abnormally large S wave in V_6 together with an abnormally tall R in aV_R , which was four to ten times the amplitude of the downward deflection in the same lead. If additional leads had been taken over the right precordium, it is probable that the diagnosis of right ventricular hypertrophy could have been definitely established in some of these cases.

(D) Incomplete right bundle branch block was present in nine patients, the diagnosis being established by the following criteria: (1) in leads from the right side of the precordium, the R wave was prominent and exhibited either a coarse notch or double peak and S wave was small or absent, whereas, in leads further to the left, S wave was deeper and broader; (2) time interval from beginning of QRS to onset of intrinsicoid deflection in V_1 that was generally between 0.05 and 0.075 second and exceeded that in uncomplicated right ventricular hypertrophy; (3) total duration of QRS that was less than 0.12 second and usually between 0.09 and 0.11 second; (4) absence of Q wave in leads from the right side of the precordium. The electrocardiographic pattern of incomplete right bundle branch block was more or less stereotyped, irrespective of the cause of the right ventricular hypertrophy.

(E) Complete right bundle branch block was present in three cases, as indicated by the following criteria: (1) in leads from the right side of the precordium the R wave was prominent and either coarsely notched or double peaked, Q was absent, and S was small or absent; (2) total duration of QRS was 0.12 second or longer. Neither complete nor incomplete right bundle branch block are pathognomonic of right ventricular hypertrophy.

(F) Pattern in the precordial and unipolar extremity leads was not diagnostic of either hypertrophy or a conduction defect in the right ventricle in seven cases. One of these patients, who had an R' deflection in V_{3R} and V_1 which was thought to have been derived from the posterobasal surface of the left ventricle, is discussed in detail.

4. The presence of right axis deviation in the standard leads accompanied by depression of RS- T_2 and RS- T_3 and inversion of T_2 and T_3 is not diagnostic of right ventricular hypertrophy, as shown by previous workers and confirmed by our autopsy material. This pattern may occur in left ventricular hypertrophy and even in normal subjects when the heart is in vertical position.

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TONOSCILLOGRAPHY AFTER EXERCISE IN PERIPHERAL VASCULAR DISEASE AND COARCTATION OF THE AORTA

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EXERCISE-TONOSCILLOGRAPHIC studies have been carried out in normal subjects, in patients with peripheral circulatory disturbances, and in patients with coarctation of the aorta. The peripheral circulatory disturbances were divided into three groups: (1) demonstrable organic arterial circulatory disturbances; (2) intermittent claudication; and (3) miscellaneous types.

Exercise tests were accompanied by an increase of blood pressure and larger pulsations in all normal subjects. In all cases with demonstrable arterial circulatory disturbances, however, an inverse reaction with decrease of blood pressure and weaker pulsations was obtained. The inverse oscillographic reaction was, on the whole, found in all cases of intermittent claudication. The other peripheral disturbances showed normal work tests.

On the basis of our experience with exercise tonoscillography,¹⁰⁻¹² this test is believed to be valuable in the early diagnosis of organic obliterating processes in the large vessels of the extremities, and may be useful for the differential diagnosis of these states and those due to functional conditions.

Repeated oscillograms with the patient at rest very often exhibit considerable variation. Oscillography after exercise, however, gives more consistent records which are easy to reproduce. Work-tonoscillography is an attempt to eliminate the uncertainty of oscillographic measurements at rest.

In order to obtain a graphic record of a work experiment by means of oscillography, an automatic blood pressure recorder has been constructed.* Apparatus of exactly the same type has not been previously described, although automatic blood pressure recorders of different construction and type are described in papers by Bergman,³ Eldblom,¹⁴ Stokvis,²⁵ Weiss,²⁶ and others.

Relatively little attention has been given to oscillography after exercise. Cornil and Parisot⁷ have referred to it. André-Thomas and Lévy-Valensi¹ have studied oscillometry after exercise and found that the pulsations become weaker or even disappeared in patients with intermittent claudication. Ipsen¹⁹ stated

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*This apparatus was demonstrated at the Society of Internal Medicine in 1943.

that after making a patient perform an exercise test he could not feel the dorsalis pedis pulse, but the pulsation returned after a minute or two. In 1941, Leary and Allen,²¹ using oscillography after exercise, registered diminished pulsations in two cases. These results they thought to be due to arterial spasm. In three other cases, however, Leary, using an oscillograph, obtained either increased or unchanged pulsations. In the German and Anglo-American literature I have been unable, as yet, to find any reports of experiments carried out with oscillography after exercise. Following my first publication in 1944, Lindqvist²² published a paper in which he reported observations on oscillography after exercise. His work involved a study of seven cases.

APPARATUS

The oscillographic records in this study were made with an automatic, graphic-recording blood pressure manometer. The apparatus is constructed so that the oscillograms are placed in a vertical position, side by side, in such a way that several oscillograms can be recorded on the same graph (Fig. 1).

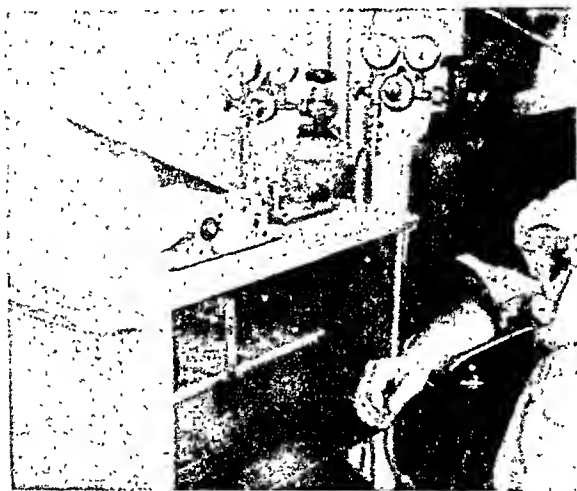


Fig. 1.—Photograph of automatic graphic-recording blood pressure manometer. The arrangement of the paper and recorder is such that oscillograms are recorded vertically. Several oscillograms can be recorded on same graph.

The apparatus consists essentially of two systems working independently of each other (Fig. 2). The one system consists of a cuff (the upper or pressure cuff), a manometer, and an oxygen tank connected with each other by rubber tubes which pass through an automatic valve. The cuff is filled slowly from the gas tank and the filling is recorded by the manometer which, by means of a lever, inscribes the cuff pressure in direct proportion. The paper on which the lever writes has horizontal lines at pressure levels in the pressure cuff of 50 mm., 100 mm., 150 mm., and so forth.

The other system consists of a second cuff (the lower or pulse cuff), a gas tank, a piezoelectric crystal, an amplifier, an electromagnet, and a movable

writing pen attached to the lever mentioned previously. By means of valves, this cuff is filled and emptied at exact intervals. The small pressure variations produced in the lower cuff by the arterial pulsations are transformed into electric potential variations by a piezoelectric crystal and are greatly amplified.

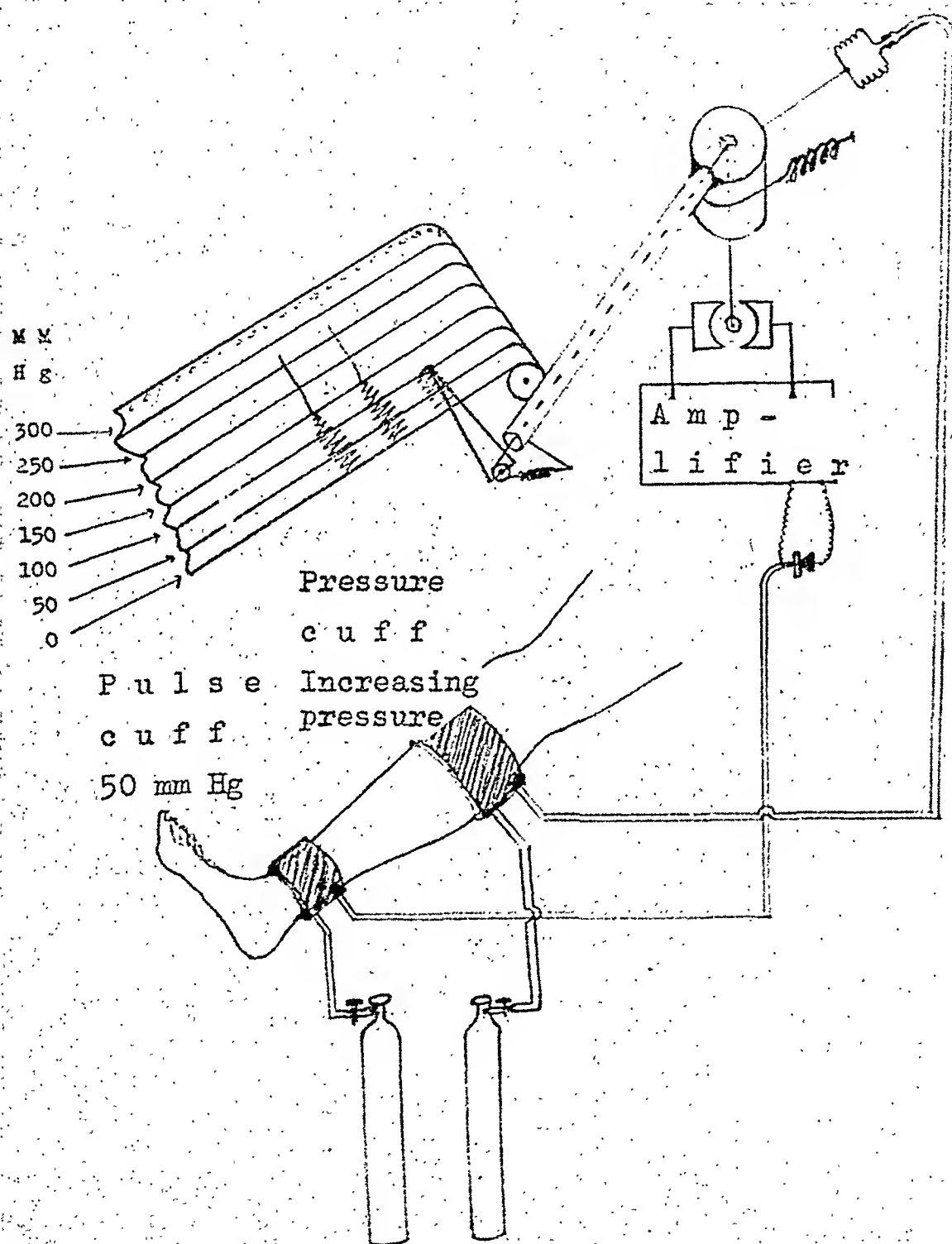


Fig. 2.—Drawing showing the connection of the two independent systems, the pulse cuff and the pressure cuff, to the amplifier and to the recorder. See text.

The registration is automatic and at each half-minute a new oscillogram is started. Each recording takes about twenty seconds. After a few seconds' pause, the next record begins. During the pause the cuffs are completely emptied so that no venous congestion can take place (Fig. 3).

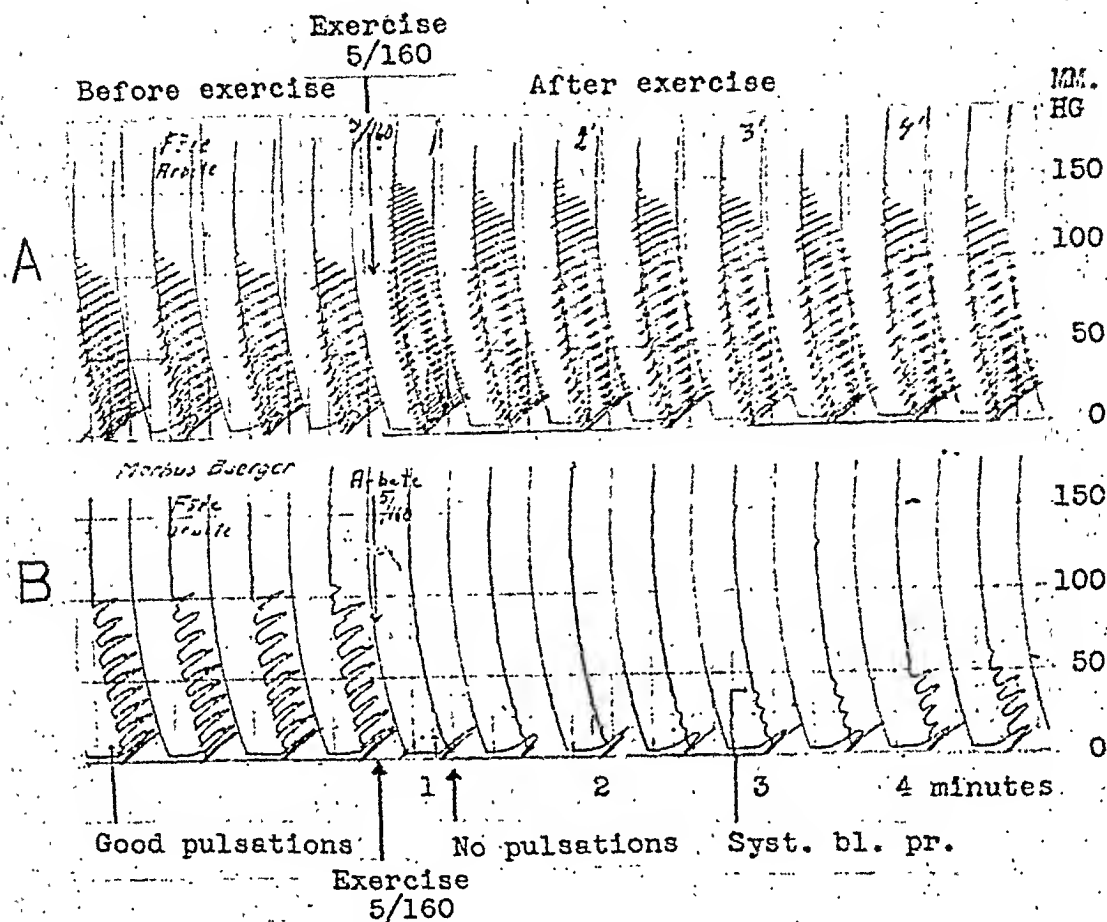


Fig. 3.—Two typical curves: A, from a normal case, and B, from a case with organic vascular changes.

In most instances, the two-cuff system was utilized, but occasionally a one-cuff system was used. The reading of the systolic and the diastolic pressure levels differs in the two systems. In the two-cuff system where, for example, one cuff is applied to the calf and the other to the ankle, the pressure increases continuously in the higher cuff (the pressure cuff) during the recording, whereas the lower cuff is immediately filled to a certain pressure, for example 50 mm., and is kept constantly at that pressure. The arterial pulsations that pass through the proximal pressure cuff are recorded by the lower cuff. It is clear that above a certain pressure in the upper cuff no more pulsations reach the lower cuff, and no further deflections are obtained from the recording lever by continued inflation of the upper cuff. The advantage of this system is that the curves are more regular and more clearly defined, and that the systolic blood pressure can be more accurately determined.

At the start of the recording, when the lower cuff has been filled to 50 mm., the pen records the pulsations at right angles to the movement of the axis of the lever. Above systolic pressure the record of pulsation ceases but the lever continues to rise, writing only in a straight line. The registration takes place during inflation of the compressing cuff and the systolic blood pressure is the level at which the pen stops its oscillations.

Change in configuration of the oscillographic pulse indicates the diastolic pressure. After having been similar for each cycle, the pulse curve begins to change its form. The position of the dicrotic notch is shifted. The initial pulse impact against the recording cuff becomes sharper, as indicated by steeper peaks. As a rule the pulse curve becomes narrower. Usually there is no difficulty in determining the diastolic blood pressure level, but in some cases, especially the pathologic ones with slow rising pulsations and low blood pressure, the same difficulties are encountered as in the auscultatory method. The transition becomes less clearly defined. In such cases the examination is made with the one-cuff system which shows the diastolic pressure more distinctly, although the systolic level becomes less definite.

THE METHOD

The patient is placed in a recumbent posture. All clothes that could cause pressure on the extremities are removed. The patient usually lies with the upper part of the body uncovered so that the proximal cuff can be applied to the arms as high as the armpits. Shoes, stockings, and trousers are removed. The room temperature is kept constant at about 20° C. All temperature variations are recorded.

The cuffs are applied to the upper or lower legs, depending on which are to be examined. In most of the cases the oscillograms are recorded from both the arms and legs for comparison. The cuffs are always applied in the same way and at the same level on the extremities. A standard cuff with a special fastening arrangement is used. The fastening process consists of metal pins arranged like steps. The particular hook by which the cuff is fastened is recorded. The circumference of the limb is recorded in centimeters at the level where the cuffs are placed. The cuffs are rather snugly applied. Each hook corresponds to a difference of 0.5 cm. in circumference.

When examining the upper limbs the proximal cuff is applied close to the armpit and the distal cuff over the antecubital fossa or the wrist. The proximal cuff for the legs is applied at the narrow section between the knee and the calf. The distal cuff is placed immediately over the malleoli with its lower edge at the level of the internal malleolus. The center part of the cuff is, therefore, at the narrowest part of the leg. The cuffs can also be applied to the thigh and calf, in which case the proximal cuff is placed immediately above the knee, and the distal cuff just underneath the knee.

When the one-cuff system is used, the cuff is applied to the small of the leg between the calf and knee, to the thigh above the knee, and higher up on the thigh in order to determine the level of the obstruction.

The patient first lies for twenty minutes in a horizontal position and his blood pressure is determined by oscillograph and auscultation. The oscillographic as well as the auscultatory values are recorded and the exercise test does not begin until the basal values are reached.

After a sufficient number of rest oscillograms have been made in horizontal position, the patient performs some exercise which usually consists of running some rounds in a circular staircase as described by Nylin.²¹ The exercise has three degrees of severity: (1) five rounds at 88 steps a minute (5/88) which is recorded as light work; (2) five rounds at 160 steps a minute (5/160), moderate work; and (3) ten rounds at 208 steps a minute (10/208), heavy work. These three procedures are used in Nylin's cardiopulmonary function tests and have been found most practical. The rate of the different tests is determined by means of a metronome. In some cases tests were made using ten rounds at 160 steps a minute (10/160), that is, in cases where the patient had difficulty in making 208 steps a minute but could very well make 160 steps. This amount of work is considerably less than 10/208 and the rate of 10/160 has, therefore, even been used in cases with coarctation of the aorta so that comparisons can be made as early as possible after the Crafoord operation.^{8,a,b,c} I have not been inclined to use the most strenuous test until one year after this operation.¹²

For comparison, the ergometer bicycle has been tried, the work being measured, however, in kilograms per minute. No difference in reaction has been observed; an inverse reaction was obtained after work on the bicycle in those cases that gave inverse reaction after exercise on the stair, and a normal reaction was obtained after work on the bicycle in those cases in which a normal reaction had been obtained after work on the stair. The bicycle has the advantages of recording the oscillogram during work, of using an extremity which is not required in the work test, and of taking up less space than the stair.

When the exercise has been completed the patient immediately resumes a horizontal position. The cuffs are applied in exactly the same way and fastened to the same hook as before the exercise. This procedure generally requires fifteen to twenty seconds. For uniformity, the recording of the initial oscillogram must be started exactly thirty seconds after the work has stopped. Thereafter, it is taken every half-minute until the blood pressure and the pulsations return to their prework values. The duration and type of the so-called recovery phase is examined and the magnitude of the oscillations before and after exercise is compared. The duration of the recovery phase is recorded in half-minutes. Herewith, one distinguishes between the restored blood pressure and the restored pulsations.

Any symptoms occurring during and after exercise are recorded, as well as the time of appearance of any pain in the calves. Peculiarities, such as limping, breathlessness, precordial pain, cardiac palpitation, and hysteriform reactions are also recorded.

Concurrently with the oscillographic recording after exercise, auscultatory blood pressure measurements are made on the other extremity or on the upper limbs and noted above the corresponding oscillogram of the registered curve.

As far as possible all cases are subjected to a study of their central circulation by means of physical examination, electrocardiogram, hypoxemia test, and x-ray examination with determination of the heart volume. In special cases measurements of the pulse wave velocity are carried out, and with a certain number of patients oscillography with optical registration has been used coincidentally with the mechanically inscribed oscillogram. The optical oscillogram was constructed by the use of one or two piezoelectric crystals connected with an electrocardiograph¹⁰ (Figs. 4 and 5).

As a rule, the studies are carried out on all four extremities, the patient being allowed to rest sufficiently long between each work test. When the blood

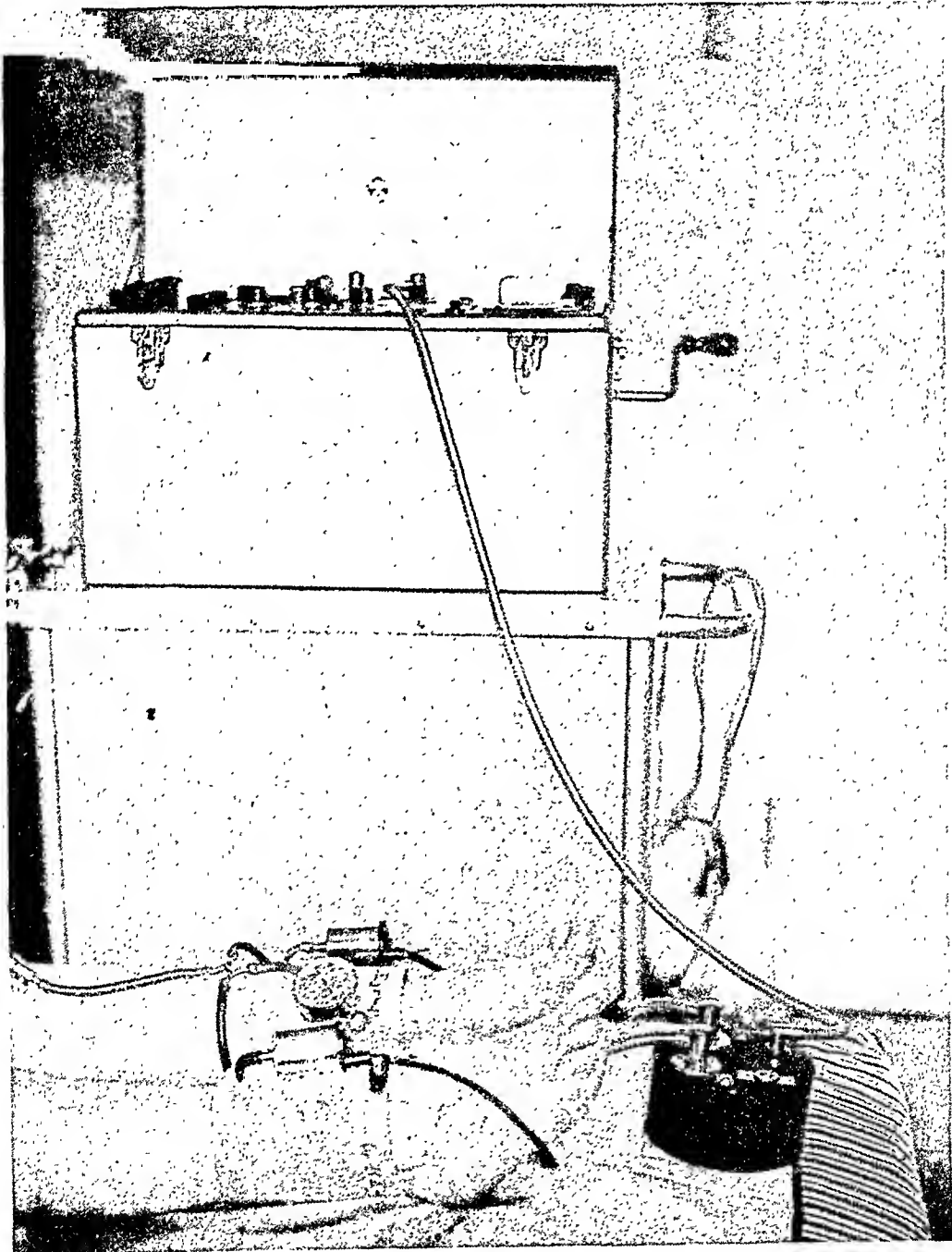


Fig. 4.—Apparatus for recording the oscillogram by optical registration. See text.

pressure and the pulsations have returned to basal values, the patient is allowed to rest an additional half-hour before the next test. There is no difference in reaction to work between a test carried out immediately after the postexercise period and a test carried out one hour later.

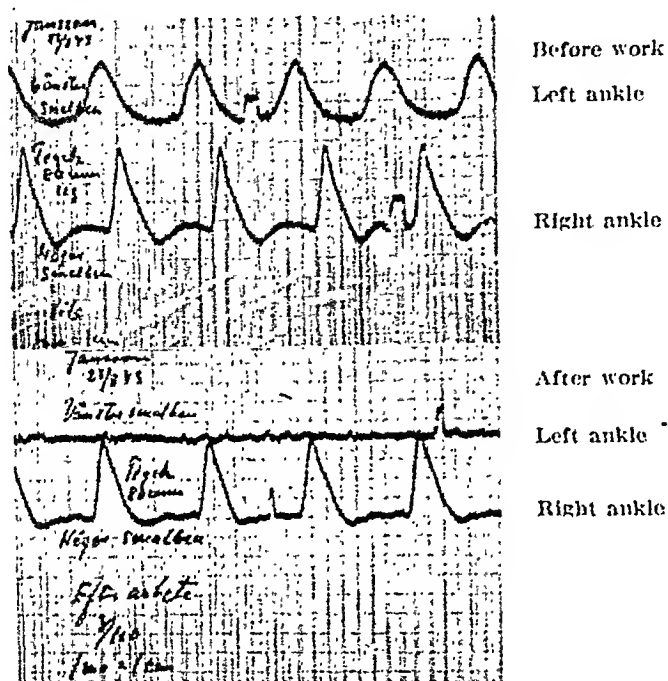


Fig. 5.—Oscillograms before and after work of a patient with organic obstruction of a large artery of the left leg (optical registration on the ECG apparatus).

Before each examination accurate history and physical examinations are recorded with special emphasis on the character of the peripheral vascular system.

RESULTS

Normal Cases.—Thirty-six normal cases have been examined. They have been divided into three groups:

Group 1 included ten postmen who were first examined in the morning before the day's work and then immediately after the day's work. The reason why postmen were chosen for study was partly because their lower limbs must be regarded as being functionally very efficient; and partly because this group can show whether there are differences in a work-oscillogram taken after a night's rest, and in one made immediately after a strenuous day in which much walking and climbing of stairs is included. None of the postmen showed any difference in the type of oscillograms made before and after the day's work. On both occasions they showed improved pulsations and raised blood pressure. The severest exercise test (10/208) was used in all cases. The first test was made at 4:30 A.M. after a night's rest, and the control test, which was carried out on the same leg and in exactly the same way, was made at 12:30 P.M. immediately

after the strenuous "second tour" was over. Oscillograms at rest were made on both occasions on both legs; the oscillograms did not differ.

This group thus gave us the following information: (1) The time at which the work oscillogram of a normal case is taken is not important; (2) strenuous work for the legs done during the day does not seem to change the reaction to the work-test; and (3) the response to exercise by postmen does not differ from that of other groups of normal cases, in spite of strenuous work.

Group 2 was composed of dancers and subjects having similar occupations (teachers of gymnastics, sportsmen). They all underwent tests on the arms and legs and all showed better pulsations and heightened blood pressure after exercise. Some have even been tested after different kinds of work. Oscillograms have thus been taken after one, two, three, and up to ten rounds with 208 steps a minute on the Nylin staircase, and similar reactions to work were obtained in all cases.

Group 3 included healthy normal subjects selected from the author's acquaintances. As a rule, oscillography on both legs and in many cases repetition of the test after longer or shorter intervals was carried out. All these cases showed the heightened blood pressure and the increased pulse amplitude after exercise which was characteristic of the other two groups.

One hundred thirty-seven work tests have thus been made on these thirty-six normal subjects and all the persons on which the experiments were made have shown similar reactions (Fig. 3, 4). On repetition of the experiments on the same person, there was always the same type of exercise response. Further tests of normal cases are in progress.

The division into three groups was made in order to show that there is no special difference in the type of work response in trained and untrained subjects. As to the raised blood pressure and the length of the recovery period, there was this difference, the blood pressure of the trained persons did not rise as high as that of the untrained, and the recovery phase was not as long.

The blood pressure was higher in all cases in the lower limbs than in the upper limbs when measured on the upper arm and calf in the horizontal position. The difference was less in younger than in older persons. The pulsations were less in the small of the legs than in the arms at the level of the elbow. A comparison of the pulsations of the small of the leg with those of the wrists showed that the pulsations of the wrists were less than those of the ankles. The index was less than one unit as Atlas has stated.²

Cases With Confirmed Structural Diseases.—When there was organic obstruction of the larger arteries of the limbs, the oscillogram after exercise showed an inverse reaction with a lower blood pressure and a decrease or absence of all the pulsations (Figs. 3, 5, 6, and 7). This inverse reaction occurred only if the oscillogram was made distal to the obstruction. When a partial occlusion was present, in the popliteal artery, for example, the oscillogram from the small of the leg showed this inverse reaction, but oscillography on the thigh above the knee and on the calf just under the knee gave the heightened blood pressure and the respective increase of the pulsations which are characteristic of normal subjects.

The inverse reaction after exercise in pathologic cases seems to be independent of the nature of the stenosing process. Thus, cases of Buerger's disease, arteriosclerosis, and postembolic states gave the same inverse reaction.

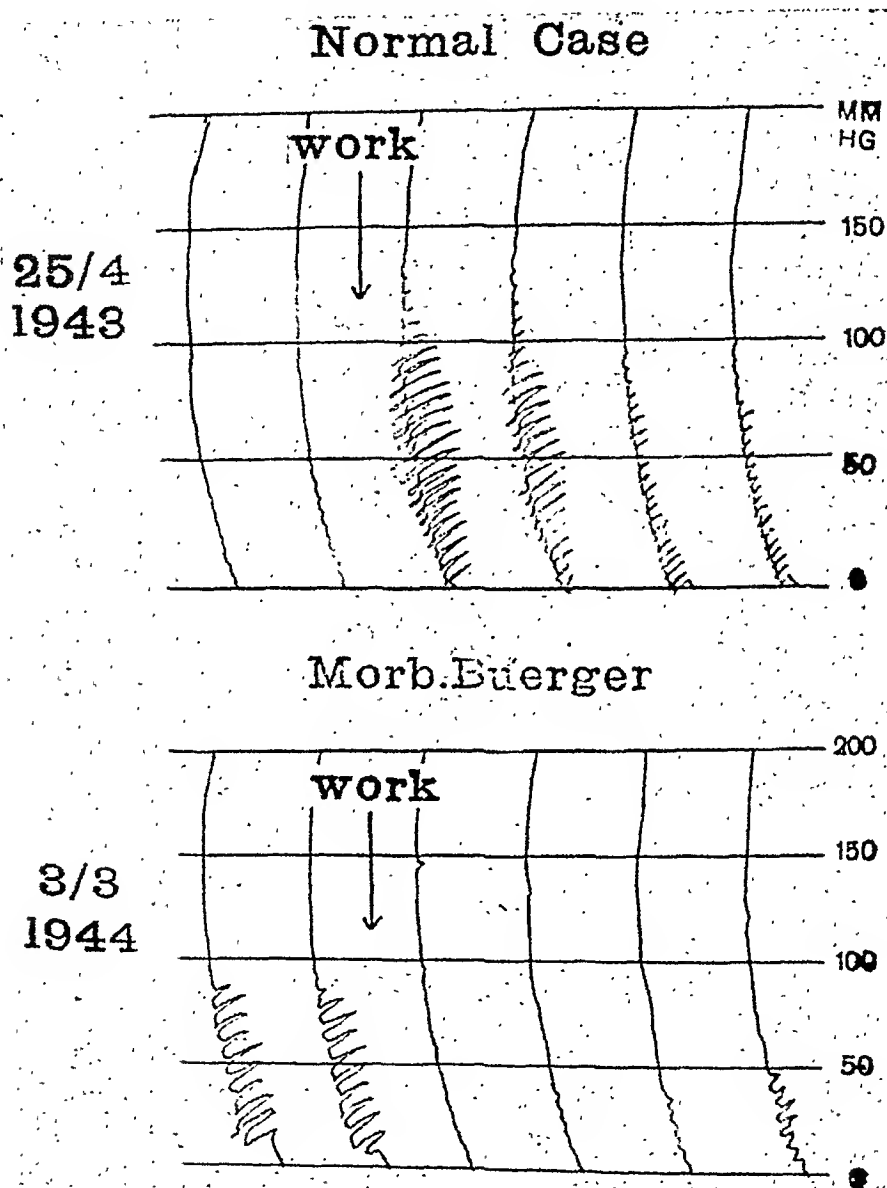
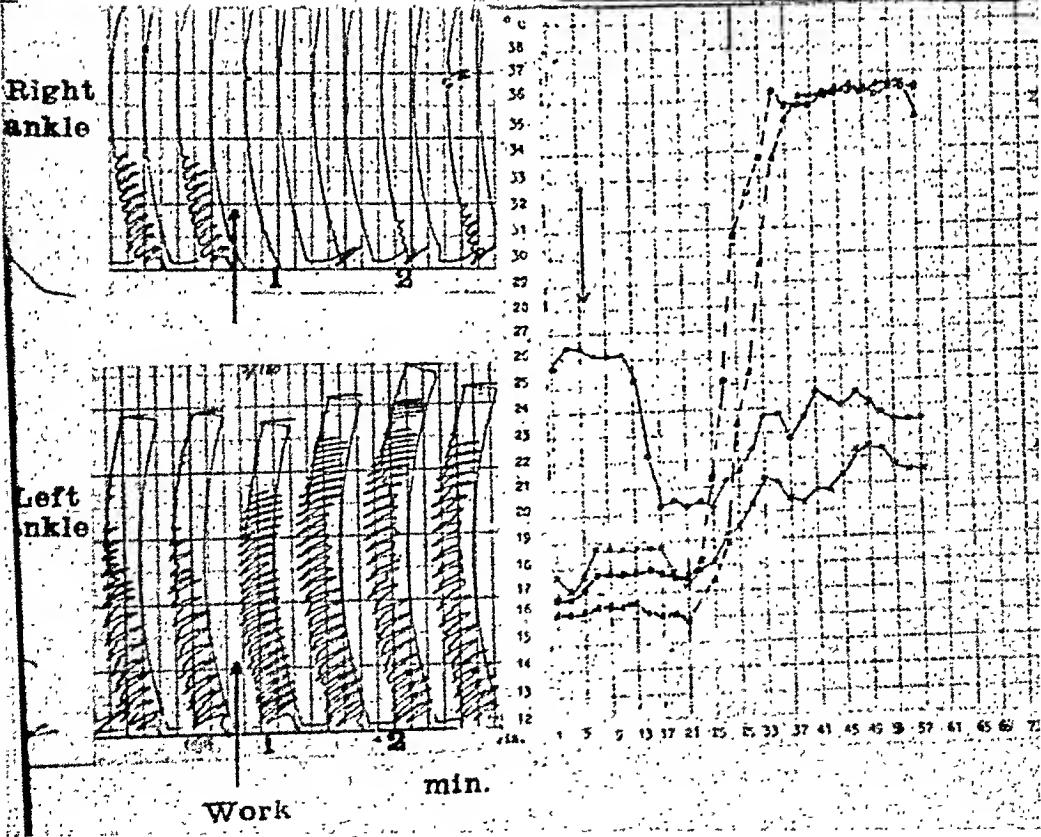
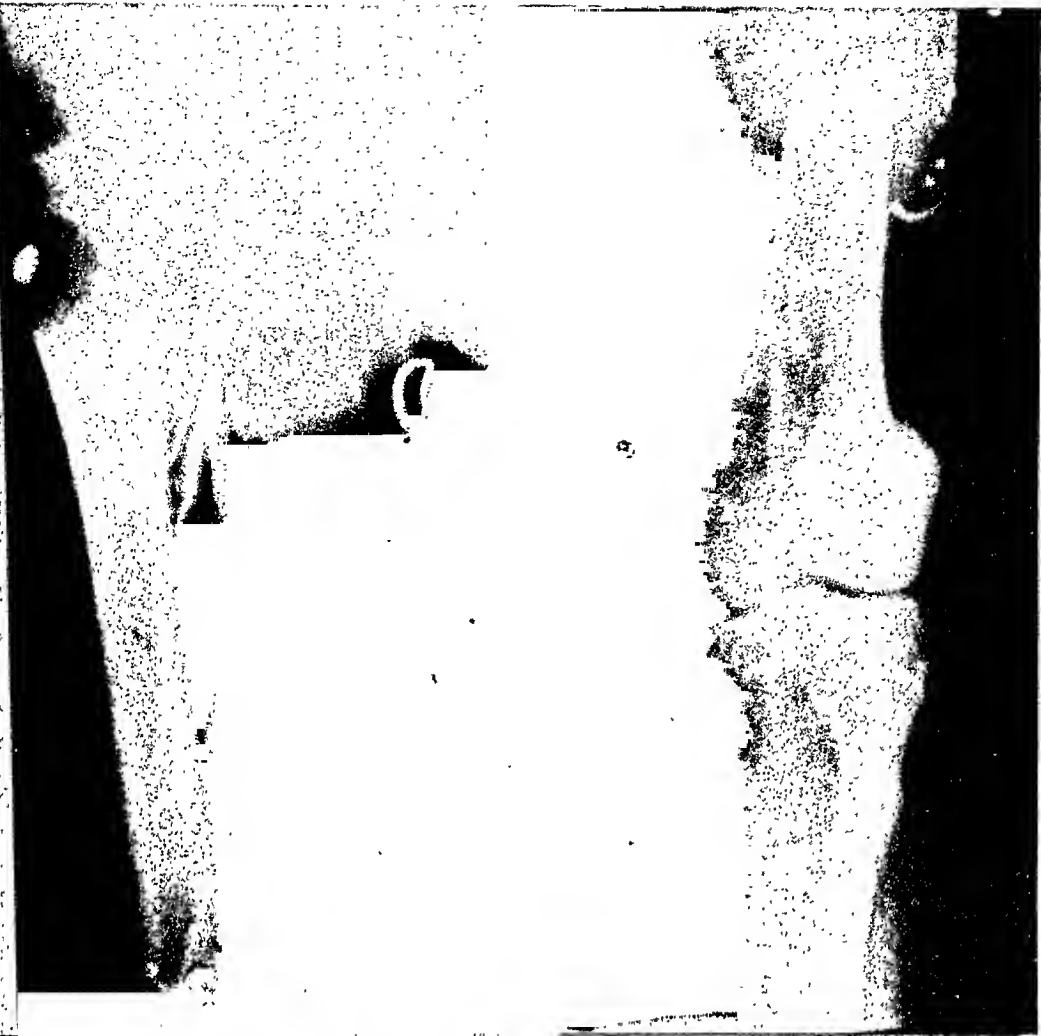


Fig. 6.—In a normal person the oscillogram at rest can show very small deflections, whereas in a person with intermittent claudication it can reveal moderately large pulsations which are better than the pulsations in a normal person. The upper oscillograms were made on a 25-year-old woman whose hobby is skiing. The lower oscillograms were made on a 45-year-old man who had Buerger's Disease. After exercise the oscillograms of these two patients changed very strikingly so that the normal subject had large pulsations whereas the pulsations of the patient with Buerger's Disease disappeared.

Only those cases of structural changes confirmed by arteriography have been included in this group (ten cases). All cases have, without exception, shown the inverse reaction after exercise. That this group contains so few cases depends partly on the fact that we do not like arteriography, and partly because

Arterio-
graphy



Skin temperature measurements after heating ∇

Fig. 7.—Oscillograms and skin temperature response in a patient with organic occlusive arterial disease of the right lower limb.

contrast media were difficult to obtain during the war. I chose to include in this group only the absolutely definite cases of organic obstruction. All others with typical clinical signs are included in the next group under Intermittent Claudication.

Intermittent Claudication.—Most patients with organic arterial obstruction exhibit intermittent claudication. This symptom is probably caused by the vessel closure even if there is a considerable degree of associated vasoconstriction. Most of the patients with claudication showed abnormal work-tonoscillograms, that is oscillograms of the type found in the previously mentioned group with structural changes. This fact should compensate for the small number of cases in the latter group.

Fifty-four patients with typical intermittent claudication were studied. All of them were subjected to work-oscillographic studies, and no less than fifty-two showed the inverse reaction to exercise. Some patients had symptoms in only one limb but nevertheless showed pathologic exercise oscillograms from both limbs. The oscillogram was always more abnormal, however, in the painful limb. Vascular changes were present in both limbs, although less in one of them. The reason the patient may not have symptoms in both limbs is that the pain in one limb prevents his performing an amount of work sufficient to produce pain on the healthier side.

These experiments show that oscillography after exercise permits an early diagnosis in cases of structural vascular change where intermittent claudication has not yet appeared but an inverse reaction can be demonstrated. This fact is obviously important from the prognostic point of view.

A number of exercise-tests were performed on these fifty-four patients, many of whom have been re-examined every year in connection with diagnostic and therapeutic procedures. It was demonstrated in those cases that it was easy to obtain consistent results which show few variations in the appearance of the recovery phase after the same exercise.

Since each of the two lower extremities represents one test object with individual reactions, depending on the state of the artery in the extremity examined, the number of exercise-tonoscillograms have been considered in relation to the number of examined extremities. This method was used since it gives statistically more reliable values than when the patient is taken as a unit. A total of ninety-eight extremities have been examined. Of these, typical intermittent claudication was present in eighty-nine. Of these claudicant limbs, eighty-five showed pathologic work-tonoscillograms. All pathologic work-tonoscillograms were obtained from extremities which exhibited claudication. Of 250 examinations after exercise which were made on claudicant limbs, 246 showed an inverse reaction.

As most of the patients in the group with intermittent claudication showed pathologic oscillograms after exercise the question arises as to what difference exists between cases of intermittent claudication which show the inverse reaction and those which do not. It appears that the two exceptional patients had served their time in the army and that their symptoms had been aggravated.

Coarctation of the Aorta.—Through the Crafoord operation^{8,2} the diagnosis of coarctation of the aorta may be confirmed, and seventeen such cases have been examined. Exercise tests were made before the first operation because many of the patients complained of intermittent limping. On examination, all of the cases of coarctation showed a typical reaction after exercise, as well as a typical oscillographic picture during rest. Characteristic of the latter is high blood pressure and large pulsations in the upper limbs, as well as low blood pressure and small pulsations in the lower limbs. After exercise, these patients showed no increased blood pressure but rather a slight drop. In some cases the pulsations were diminished or even absent. In other cases there was a slight increase in the size of the pulsations. None of the seventeen cases examined, however, showed a normal reaction after exercise from the lower limbs (Fig. 8, left).

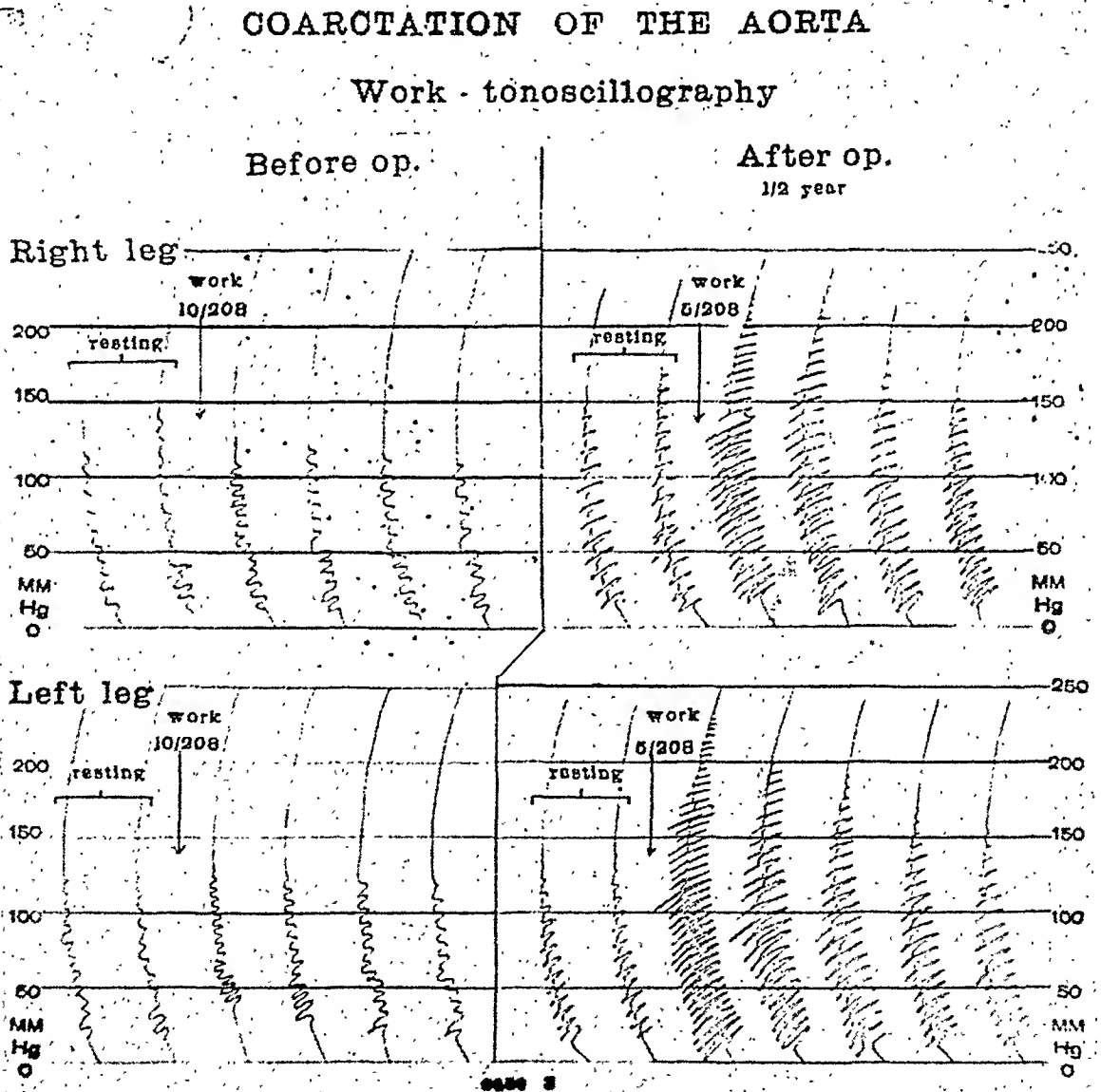


Fig. 8.—Work-oscillograms of both lower limbs before and after operation in a patient with coarctation of the aorta.

The exercise-oscillographic test was used in these cases to confirm the diagnosis. It was also of great interest to observe how, after the Crafoord operation,^{8,a} with resection of the stenosed section of the aorta and end-to-end anastomosis, the circulation was re-established and normal exercise tests could be obtained from the lower limbs (Fig. 8, right). The examination of patients with coarctation has emphasized the accepted hypothesis that exercise-oscillography gives an inverse reaction when there is organic obliteration of the large arteries. The inverse reaction disappeared after the coarctation was corrected.

The Remaining Cases.—The remaining group tested with oscillography after exercise comprised 310 cases. The patients were of different ages and their complaints arising from the lower limbs included paresthesias, joint pains, neuritic manifestations, fatigue, and flat feet. In this group there were no patients with typical intermittent limping. Some of the patients suffered from chronic carbon monoxide poisoning with pains in the lower limbs, and quite a number had the typical symptom of "restless legs."¹³ Usually, both legs were examined but none of the patients in this group showed any inverse reaction on work.

DISCUSSION

The rise in blood pressure during and after exercise in normal subjects has been known a long time and has been pointed out by several authors. The increase in size of pulsations in the upper limbs after exercise has also been described and demonstrated on the oscillogram.^{6,15} The decrease in size of the pulsations in the lower limbs after exercise in pathologic cases, on the other hand, has been the subject of study by only a few authors. Christensen⁶ studied the reaction in patients with effort angina and the effect of hyperventilation. André-Thomas and Lévy-Valensi,¹ Leary and Allen,²⁰ Ejrup,^{10,11} and Lindqvist²² have made oscillographic studies on cases of claudication. Lowering of the blood pressure after work in cases of cardiac insufficiency has been noted in the upper limbs by Grebner and Grünbaum,¹⁷ Masing,²³ and others. As to the fall of blood pressure after exercise in the lower extremities in the presence of stenosing disease of the larger arteries, I could find no special reference in the literature. It should be emphasized that the lowered blood pressure is a finding which is quite as important as the decrease of pulsations. The syllable, "ton," in the expression "exercise-tonoscillography" indicates that in addition to the size of the pulsations, the height of the blood pressure is also obtained from the written oscillogram.

It is of interest to discuss the conditions which produce the pathologic work oscillogram. Is it spasm in the artery, or is there another cause for the fading pulsations? Different opinions regarding the explanation of intermittent claudication are found in the literature (Charcot,⁹ Erb,¹⁶ Lewis and associates,²¹ and Hustin¹³). The author is inclined to believe that collateral spasm is one of the causes of the absent pulsations. In many cases the main artery is narrowed or obliterated and the blood supply is maintained only through collateral channels. This is true, for example, in a number of cases of coarctation, but it can also be clearly demonstrated in peripheral circulatory derangements. Neverthe-

less, there are distinct pulsations recorded by oscillography: These pulsations arise from the collateral vessels. The collateral vessels are dilated arteries or capillaries with a structure that does not coincide with the function they perform. Another factor is their superficial position. The collaterals are not enclosed in arterial sheaths between the muscle bundles but cross these muscle bundles more or less lengthwise. They are thereby exposed to an influence which, in combination with their weaker structure, increases their tendency to spasm. When spasm of the collaterals occurs and the principal artery is more or less obliterated, all the pulsations vanish distal to the level at which the collaterals traverse the muscles. In cases of coarctation, where the occlusion is complete and the lower half of the body is supplied solely through the collaterals, exercise-oscillography shows diminished pulsations in the legs where normal or increase of pulsations due to compensatory dilatation, might be anticipated. This phenomenon is most likely caused by vasoconstriction in the collaterals.

This collateral spasm theory should apply unreservedly to those cases where the main artery is completely obliterated. In other cases with a partially obliterated main artery, the same thing can happen, but there should be an increased tendency to spasm also in the pathologically altered main artery.

On examination of the structural changes of the peripheral arteries, as in cases of coarctation of the aorta, both the systolic and the diastolic pressures fall in the legs after exercise. This could be due partly to the fact that the blood is pumped away from the muscles through the intact venous system, the obliteration of the arteries, meanwhile, hindering the inflow. If the venous outflow were checked, the local situation should be improved. Experiments with permanent venous congestion in those cases are in progress. Intermittent venous congestion in claudication cases have already been tried with good results.^{4,5} Permanent venous congestion has been produced by operation in cases of angina pectoris. There seems to be no contraindication to establishing a slight permanent congestion in cases with peripheral disease during walking. On making exercise tests with and without induced venous congestion, the test with congestion has caused less discomfort and better function. A patient who could only walk for three minutes at a certain rate, when an inflated cuff was applied to the limb, walked for nine minutes at the same rate and had to stop because of breathlessness.

The cause of the inverse oscillographic reaction to work in pathologic cases is probably quite complicated, but at least three possibilities mentioned previously should be considered: (1) collateral spasm; (2) arterial spasm; and (3) capillary bed evacuation.

The exercise-tonoscillographic test is convenient and useful in evaluating various therapeutic measures. Parallel with subjective recovery in the case of intermittent claudication, the exercise-oscillographic test shows a gradual improvement with better pulsations, higher blood pressure, and a shortened postexercise period.

In several cases with pain and definite organic vascular disease in one limb, an abnormal exercise-oscillogram has demonstrated early organic changes in the

asymptomatic limb. The decrease of blood pressure, for instance, is less marked and there is only moderate or no reduction of pulsations. In some cases there is a distinct reduction of the pulsations without a decrease in blood pressure. The test gives evidence of disease before the occurrence of subjective symptoms. The inverse oscillographic reaction appears much earlier than the pains in the calf. If the work is forced in such a case, typical symptoms of intermittent claudication appear concomitant with further pathologic change in the exercise-oscillogram. No normal subject has shown a decrease of blood pressure or reduction of the pulsations one-half minute after exercise. All cases of vascular disease, on the other hand, have shown changes ranging from absent pulsations and decrease of blood pressure to zero in the injured limb to normal reactions in the healthy limb. The test ought, therefore, to constitute an objective index of the efficiency of the vascular system in the limb examined. Compared to other diagnostic tests, exercise-tonoscillography is the simplest and also gives the earliest information concerning the functional capacity of the vessels.

The author has not been able to find any difference between cases of arteriosclerotic obstruction, typical Buerger's disease, and postembolic occlusion of the large vessels. The type of the inverse reaction apparently varies with the degree of obstruction and the development of the collateral circulation. The differential diagnosis between the previously mentioned conditions is not aided by this test. On the other hand, the inverse reaction seems to be associated with the presence of an organic obliteration and the test is thus applicable in the differential diagnosis between functional and organic conditions.

SUMMARY

A method for automatic oscillographic blood pressure recording is described. By this method oscillograms can be taken in succession without any venous congestion in the examined limb. The oscillograms are written vertically on an endless paper perpendicular to the length of the roll so that variations of the blood pressure and pulsations can be observed easily. The apparatus is especially suited for the taking of oscillograms after exercise when several successive oscillograms are required to record the type and length of the postexercise period.

The procedure involved in exercise-oscillography is described. Oscillograms are first taken with the patient at rest in the horizontal position. Work tests are then carried out on the Nylin stairs or an ergometer bicycle, after which the oscillograms are repeated in the horizontal position during the postexercise period. In normal cases an increase of blood pressure and pulsations is observed after exercise, whereas in cases in which organic vascular changes have been demonstrated and in cases of typical intermittent claudication, an inverse reaction with decrease of blood pressure and lowering of the pulsations is obtained in the lower limbs.

In cases of coarctation of the aorta, a pathologic reaction occurs with no increase of blood pressure. In some cases the pulsations are diminished while in others they may be slightly improved. This pathologic reaction disappears after operation and the oscillographic picture at rest and after exercise becomes normal.

Cases of vague symptoms arising in the legs which do not constitute true intermittent claudication show, with few exceptions, a normal oscillogram after exercise.

The pathogenesis of the abnormal exercise-tonoscillogram is discussed and the value of exercise-tonoscillography in the early diagnosis of organic peripheral arterial circulatory disturbances is pointed out. Its value and importance in the differential diagnosis between structural and functional changes of the arteries are considered.

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VARIATIONS IN THE DEVIATIONS OF S-T IN ANTERIOR WALL INFARCTION

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INFARCTION of the anterior wall in the early stage is characterized by upward displacement of S-T in Lead I and by downward movement of S-T in Lead III. In the presence of posterior wall infarction, the direction of the displacement of S-T in Leads I and III is the reverse. The reciprocal deviations of S-T may be of the same magnitude in Leads I and III. In some cases of anterior wall infarction, the elevation of S-T in Lead I is more marked than is the depression in Lead III. In other instances upward displacement of S-T in Lead I is slight and well within the normal range, whereas depression of S-T is marked in Leads II and III. Occasionally, depression of S-T is observed even in Lead I in the very early stage of anterior wall infarction. Similar variations are seen with infarction of the posterior site. The varying deviations of S-T seem to depend largely on the site and extension of infarction. Since, by taking multiple chest leads, these factors readily can be determined in the presence of anterior wall infarction, but not in infarction of posterior location, only cases of anterior wall infarction are included in this study.

CASE REPORTS

CASE 1.—B. L., a 56-year-old man, suffered an attack of severe substernal pain associated with sweating on July 20, 1943. The attack was followed by a fall in blood pressure and increase in sedimentation rate. The further course was uneventful.

An electrocardiogram (Fig. 1, A) was obtained on the day of the attack. It showed in Lead I depression of the S-T junction and a diphasic T wave. In Lead III there was very slight elevation of S-T and the T wave was unusually high. Lead CF_2 showed a QS deflection with a rudimentary R wave; the S-T junction was elevated and the T wave upright. Elevation of S-T was even more marked in Lead CF_3 . On the other hand, Lead CF_4 showed marked depression of S-T and almost complete inversion of T.

Another electrocardiogram (Fig. 1, B) was obtained three weeks after the attack. The deviations of S-T had largely subsided and had given way to sharp inversion of T in Lead I and in the chest leads. A tracing taken seven months after the attack (Fig. 1, C) showed almost complete reversion of the previous changes to normal.

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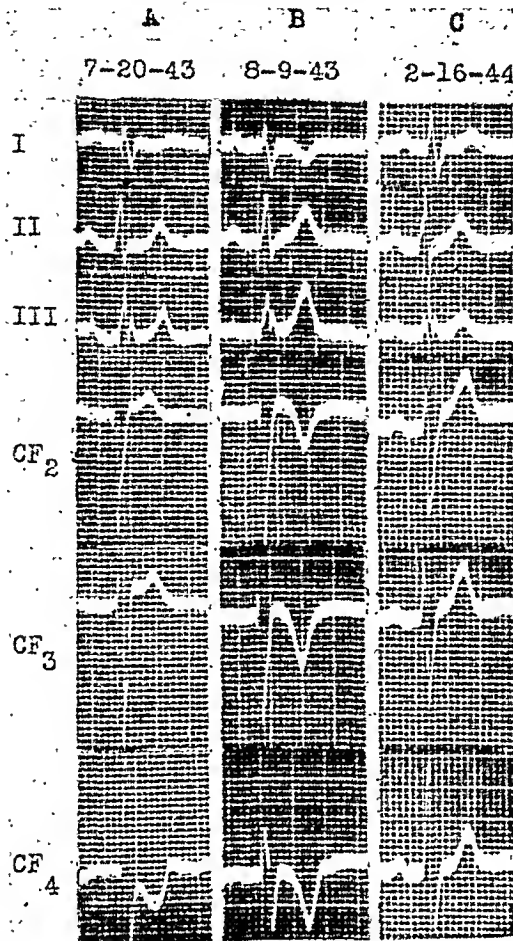


Fig. 1.—Case 1. Anteroseptal infarction (proven by necropsy). A, On the day of the coronary attack. Elevation of S-T in Leads CF₂ and CF₃ is accompanied by depression of S-T in Lead CF₄ and Lead I. B, Nineteen days after the attack. Sharp inversion of T in Lead I and in all chest leads. C, Return to normal.

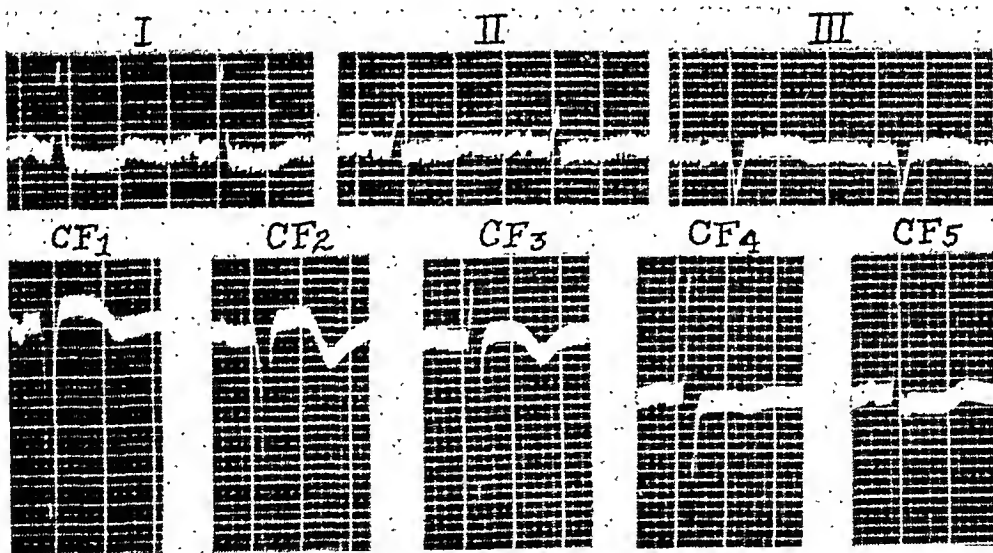


Fig. 2.—Case 2. Three days after a coronary attack. Signs diagnostic of anteroseptal infarction. Elevation of S-T in leads from the right side of the precordium is accompanied by depression of S-T in chest leads from the left side and in Lead I.

The patient died suddenly two and one-half years after the coronary attack of July, 1943. Post-mortem examination revealed an old, recanalized thrombus in the anterior descending coronary branch. An irregularly formed scar of dense fibrous tissue was found in the anterior wall of the left ventricle close to the interventricular septum.

Summary.—In the early stage of antero-septal infarction (proven by necropsy two and one-half years later) the electrocardiogram showed elevation of S-T in leads from the right side of the chest, and depression of S-T with almost complete inversion of T in the lead from Position C₄. In Lead I, as in Lead CF₄, the S-T junction was depressed and the T wave was almost completely inverted.

CASE 2.—R. P., an 86-year-old woman, had had high blood pressure for the past few years and had often felt substernal pressure on exertion. On June 28, 1946, the patient suffered an attack of protracted precordial pressure accompanied by dyspnea and wheezing. She was admitted on the following day to the hospital. Low-grade fever developed after the attack and lasted for four days.

An electrocardiogram was taken three days after the attack (Fig. 2). It showed in Leads CF₁ and CF₂ deep QS deflections, elevation of S-T, and inversion of T. In Leads CF₄ and CF₅, and also in Lead I, the S-T segment was depressed and the T wave diphasic.

Summary.—The electrocardiogram showed signs of antero-septal infarction. Elevation of S-T in leads from the right side of the precordium was accompanied by depression of S-T in leads from left-side positions and in Lead I.

CASE 3.—S. W. was a 45-year-old man. During the past two months he had suffered from "indigestion pain" which occurred frequently after meals. On May 23, 1943, he developed severe and protracted chest pain, but continued working. Two days later there was an even worse attack which was accompanied by shock.

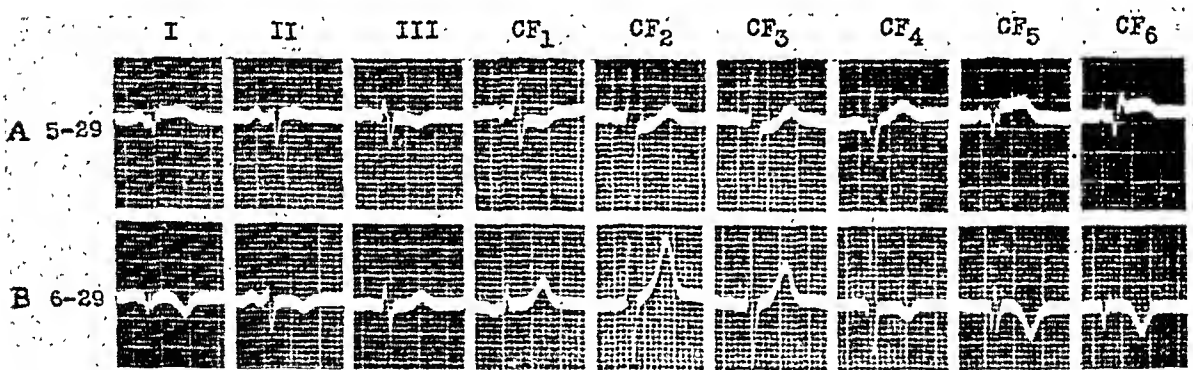


Fig. 3.—Case 3. Signs diagnostic of recent lateral wall infarction. A. Four days after the coronary attack. Elevation of S-T in leads from the left side of the precordium and in Lead I is associated with depression of S-T in leads from the right side and in Lead III. B. One month later. Sharp inversion of T in Leads I and II and in the leads from the left side of the precordium. Note the marked increase in the amplitude of R and T in Leads CF₂ and CF₃.

The first electrocardiogram was taken four days after the last attack of pain (Fig. 3, A). It showed in Leads CF₅ and CF₆, and also in Lead I, a deep Q wave and elevation of S-T. Depression of S-T was present in Leads CF₁ through CF₃ and in Lead III. In a tracing taken a month later (Fig. 3, B), the deviations of S-T had disappeared. There was sharp inversion of T in Lead I and in Leads CF₅ and CF₆. A striking increase in the amplitude of the R and T waves was noted in the leads from the right side of the precordium.

Summary.—The electrocardiogram indicated recent infarction of the lateral wall. An early tracing showed elevation of S-T in leads from the left side of the chest and in Lead I, accompanied by depression of S-T in leads from right-side positions and in Lead III. In a later stage, when deviation of S-T had disappeared, inversion of T in leads from the left side of the chest was associated with marked increase in the amplitude of the R and T deflections in leads from the right of the precordium.

CASE 4.—G. D. was a 72-year-old man. On July 8, 1945, while walking, he was seized with severe substernal pain which radiated to the neck. He perspired and felt nauseated. He came to the accident dispensary and was admitted. Physical examination revealed no abnormal findings. On the next day there was marked fall in blood pressure.

The first electrocardiogram was taken three and one-half hours after the onset of the attack (Fig. 4, A). There was left axis deviation. QRS was slurred and 0.12 second in duration. No significant deviation of S-T was noted in the limb leads. In the chest leads, the S-T segment was abnormally elevated in Lead CR₆ and abnormally depressed in Leads CR₁ through CR₅.

The second electrocardiogram (Fig. 4, B) was obtained nine hours after A. Elevation of S-T was diminished in Lead CR₆; Leads CR₁ through CR₅ showed, instead of depression, slight elevation of S-T. The voltage of T had decreased in all leads, but the decrease was greatest in Lead I and in Leads CR₄ through CR₆. The next tracings (Fig. 4, C, D, and E) showed a fairly significant Q wave in Lead I and progressive inversion of T in Leads I and CR₄ through CR₆. Temporarily, in tracing C, there was shallow inversion of T₂ and T₃.

Summary.—The electrocardiogram suggested recent lateral wall infarction. An early tracing, taken three and one-half hours after onset of the coronary attack, showed elevation of S-T in leads CR₅ and CR₆ and marked depression of S-T in the leads from the right side of the precordium. The depression of S-T was no longer present twelve hours after the onset of the attack. No significant deviations of S-T were noted in the limb leads. (Possibly there was also an old anteroseptal infarction, which is suggested by small R deflections in Lead CR₂.)

CASE 5.—J. G., a 58-year-old man, suffered from mild shortness of breath for several weeks prior to admission. He did not complain of anginal pain. He was hospitalized because of increasing fullness in the upper abdominal region. The heart was moderately enlarged. The blood pressure was 138/80. There was slight increase in venous pressure. The temperature was normal. The patient died suddenly six days after admission during a roentgenologic examination of his gastrointestinal tract.

An electrocardiogram (Fig. 5) was obtained six days prior to death. In Lead I it showed a small Q wave coupled with a low R deflection; the S-T junction was only inconspicuously displaced downward and the T wave was slightly inverted. In the chest leads, the R deflection was strikingly low in Lead CR₃; in Leads CR₄ and CR₅ a small Q wave was accompanied by R deflections of normal amplitude; the S-T segment was markedly depressed and the T wave diphasic; there were rather high T waves in Leads CR₂ and CR₃.

Post-mortem examination revealed arteriosclerosis in all main branches of the coronary arterial tree. The left coronary artery was markedly narrowed in the proximal portion, and its circumflex branch was occluded by calcific deposits. Extensive scarring was found in the anteromedial aspect of the left ventricle. A recent infarction in the anterolateral wall extended from base to apex. It did not include the subepicardial muscle layers.

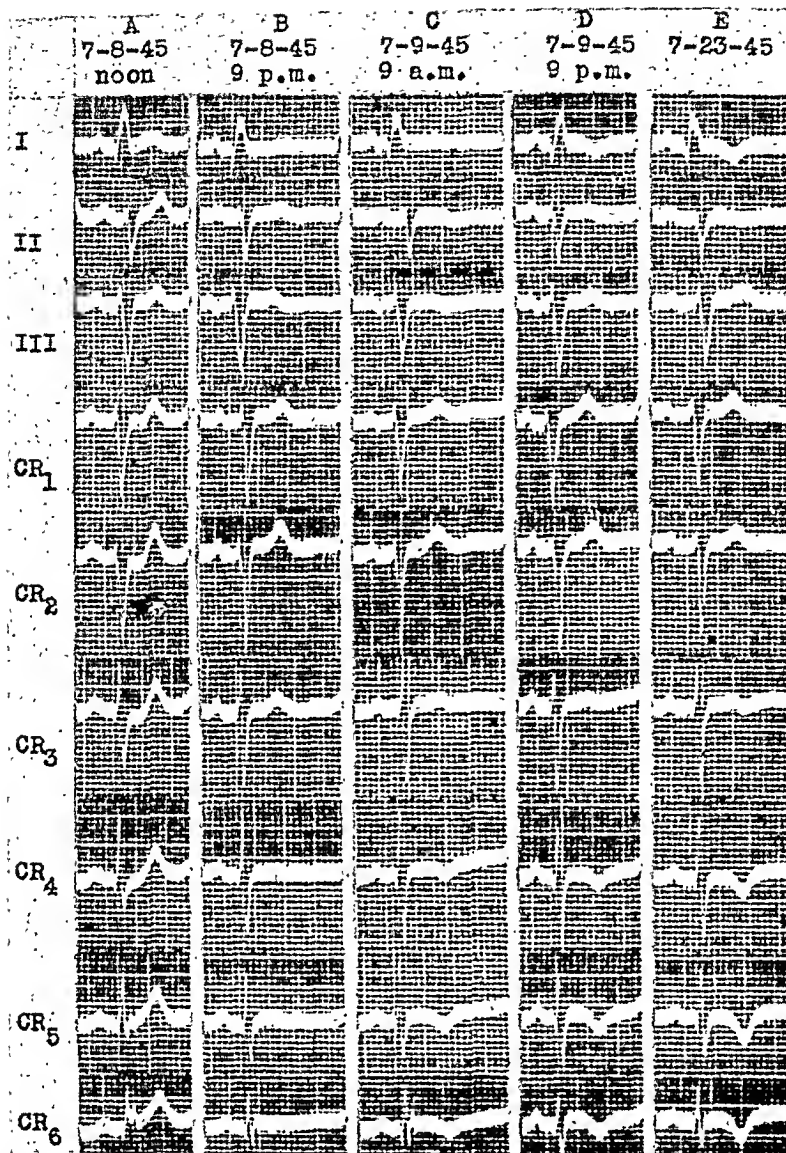


Fig. 4.—Case 4. Signs of recent lateral wall infarction. A, Three and one-half hours after the onset of the coronary attack. Elevation of S-T in Leads CR₅ and CR₆ is accompanied by depression of S-T in Leads CR₁ through CR₃. B, Eighteen hours after the onset of the attack. Elevation of S-T in Leads CR₅ and CR₆ has decreased. Depression of S-T in Leads CR₁ through CR₃ has given way to slight elevation. C, D, and E, Progressive inversion of T in Leads I and CR₄ through CR₆. In all tracings the R deflection in Lead CR₂ is strikingly low; this may be a residual of old anteroseptal infarction.

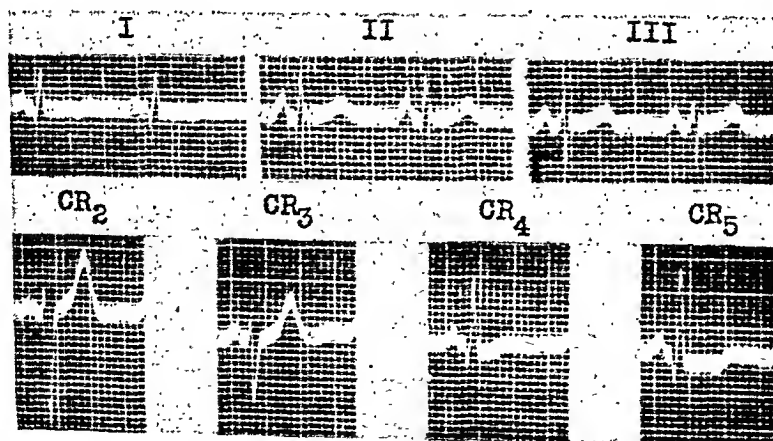


Fig. 5.—Case 5. Recent anterolateral infarction extending from base to apex, not involving the subepicardial muscle layers (proven by necropsy). Marked depression of S-T in Leads CR₄ and CR₅. The T wave is high in Lead CR₂. Lead I presents a small Q wave coupled with a low R deflection; depression of S-T is inconspicuous; T₁ is mainly inverted.

Summary.—Depression of S-T in Leads CR₄ and CR₅ was apparently due to extensive recent infarction in the anterolateral wall (shown by necropsy) which did not include the subepicardial muscle layers. Also high T waves in leads from the right side of the chest were explained by the presence of lateral wall infarction.¹ A small R wave in Lead CR₃, which was lower than the R deflection in Lead CR₂, was the only indication of scarring in the anteromedial aspect of the left ventricle which was found at necropsy.

CASE 6.—C. G., a 63-year-old man, was admitted to the hospital on May 27, 1943, because of hematuria. On the following day, while cystoscopy was being performed, the patient experienced severe substernal pain. The attack was followed by rise in temperature. Death occurred three days after the attack.

An electrocardiogram was taken five hours after the onset of the attack (Fig. 6, A). In Lead I it showed inconspicuous elevation of the S-T junction and straightening of S-T. In Leads II and III marked depression of S-T and inversion of T were present. The chest leads showed signs of recent anterior wall infarction, that is, QS deflections, elevation of S-T, and T waves of marked amplitude.

In another tracing obtained a day after the attack (Fig. 6, B), T₁ was flat. In the chest leads the amplitude of T had decreased and a terminal dip was noted in the T waves.

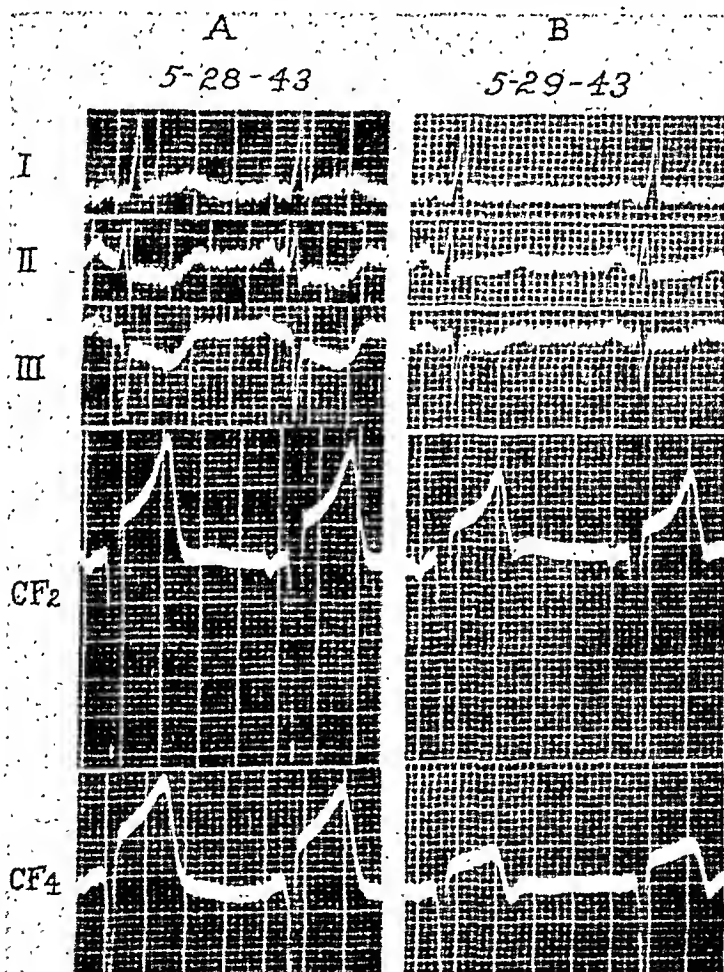


Fig. 6.—Case 6. Extensive recent infarction involving the anterior portion of the interventricular septum and adjoining parts of the anterior wall of the left ventricle. The subepicardial muscle layers are involved (proven by necropsy). A, Five hours after onset of the coronary attack. Leads CF₂ and CF₄ show QS deflections, marked elevation of S-T, and high T waves. In Lead I, elevation of the S-T junction is inconspicuous and contrasts with marked depression of S-T in Leads II and III. B, One day later. The amplitude of the T waves in Lead I and in the chest leads has decreased. In Leads CF₂ and CF₄ there is a terminal dip of the T wave.

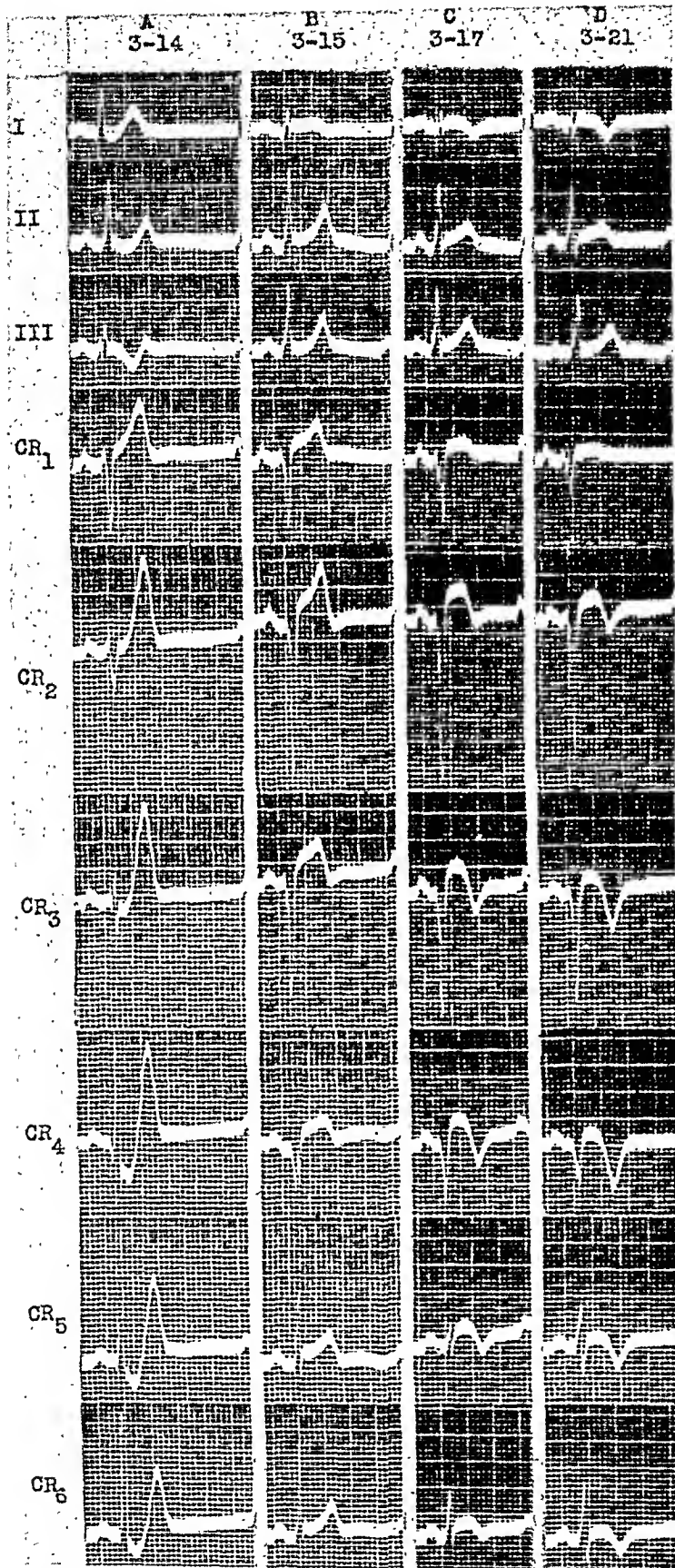


Fig. 7.—Case 7. Recent anteroseptal infarction. A, Three hours after onset of the coronary attack. In Leads I, II, and CR₃ through CR₆ marked depression of S-T is associated with unusually high T waves. No significant changes of QRS. Signs of subepicardial muscle injury (high T waves) are here superimposed on signs of subendocardial injury. B, Eighteen hours after onset of the attack. Depression of S-T is replaced by abnormal elevation. Characteristic changes of QRS and T indicate anteroseptal infarction. C and D, Progressive inversion of T in Lead I and in the chest leads.*

*This case is also referred to in Dressler, W., and Roessler, H.: "High T Waves in the Earliest Stage of Myocardial Infarction," *AM. HEART J.* 34:627, 1947, Fig. 3.

Post-mortem examination revealed extensive recent myocardial infarction, which involved the anterior portion of the interventricular septum and a large adjacent area of the anterior wall of the left ventricle. At several spots, necrosis extended to the subepicardial muscle layers.

Summary.—The electrocardiogram indicated recent infarction of the anterior wall. Although leads from Positions C₅ and C₆ were not available, the absence of significant changes in Lead I suggested that the lateral wall was not involved. This was proven at post-mortem examination. In the limb leads there was striking incongruity between marked depression of S-T in Leads II and III and the lack of significant elevation of S-T in Lead I.

CASE 7.—L. C. was a 36-year-old man. In the latter part of November, 1945, he was suddenly seized with an attack which gave the sensation of his having been "hit in the epigastric notch." Three days later, while working, he had what he considered to be indigestion with distress in the epigastric region. During the first half of March, 1946, there were similar attacks which were unrelated to intake of food. They lasted from ten to fifteen minutes. At 2 P.M. on March 14, 1946, the patient experienced a burning sensation behind the sternum, vomited, and felt weak. He was presently brought to the accident dispensary and still complained of a squeezing and burning sensation behind the sternum. The blood pressure was 90/70. The white blood count was 17,100. The sedimentation rate was normal on the day of attack. On the following day the temperature rose and remained above normal for nine days. There was increase of the sedimentation rate on the fourth day after the attack.

An electrocardiogram was taken three hours after the onset of the severe attack on March 14, 1946 (Fig. 7, A). It showed no significant abnormalities of QRS. The most striking change was marked depression of S-T in Leads CR₃ through CR₆. S-T depression was present, but less marked in Leads I and II. The depression of S-T contrasted with an unusual increase in the amplitude of the T waves, which was especially noticeable in the chest leads.

In the second tracing (Fig. 7, B) taken eighteen hours after the onset of the attack, depression of S-T had given way to marked elevation. There was a significant Q wave in Lead I. In Leads CR₃ through CR₄, the R deflection had almost disappeared. The amplitude of the high T wave had decreased and a terminal dip of T appeared in Leads I, and CR₃ through CR₄.

Tracings C and D, taken three and seven days, respectively, after the attack, showed progressive inversion of T in Lead I and in the chest leads.

Summary.—An electrocardiogram taken three hours after the onset of a coronary attack presented unusual features, namely, marked depression of S-T coupled with unusually high T waves in Leads I, and CR₃ through CR₆. Eighteen hours after the onset of the coronary attack, depression of S-T had given way to elevation, and the electrocardiogram presented the typical features of anteroseptal infarction.

COMMENT

Recent experimental findings have improved our understanding of the variable deviations of S-T observed in myocardial infarction. It has been long known²⁻⁵ that elevation of S-T is associated with damage of the subepicardial muscle layers, while injury to the subendocardial muscle results in depression of S-T. In animal experiments, Wolferth and associates⁷ showed, in direct leads from the surface of the heart, that injury to the subepicardial muscle beneath the exploring electrode caused elevation of S-T. When, however, the exploring electrode was placed at a site removed from the area of superficial

muscle injury, depression of S-T was observed. The reversal in direction of the deviation of S-T was often abrupt when the exploring electrode was moved from damaged to undamaged myocardial areas, and depression of S-T was obtained even from points on the surface of the heart remotely located from the area of damage. There was also depression of S-T when injury was confined to the subendocardial muscle layers beneath the exploring electrode placed on the surface of the heart. All of these deviations of S-T occurred regardless of whether the injury was caused by mechanical, chemical, or thermal influence, or by interference with the blood supply to the heart muscle.

The changes of S-T that resulted from complete or partial obstruction of a coronary artery are of particular interest for clinical problems. Wolferth and associates⁷ observed that after complete obstruction of a coronary branch, there was elevation of S-T in direct leads from the surface of the area deprived of blood supply. When the electrode was moved to muscle portions with unrestricted blood flow, depression of S-T was noted, and reversal in the direction of deviation was often abrupt at the margin of the ischemic muscle area. Partial obstruction of a coronary artery caused either no deviation of S-T or upward displacement, depending on the degree of interference with the blood flow. In some experiments, however, partial obstruction produced depression of S-T in direct leads from both the surface of the area partly deprived of its blood supply and from surrounding, apparently normal myocardium. When the degree of obstruction was increased, negative displacement of S-T turned into positive deviation. On the other hand, when complete or partial obstruction had caused upward movement of S-T and the blood flow was then restored to normal, there was depression of S-T for a short period before the S-T segment returned to its original level. The authors thought this was due to selective involvement of the subendocardial muscle layers. Clinically, it has been known that infarction confined to subendocardial muscle layers was characterized in the electrocardiogram by downward deviation of S-T in limb and chest leads.⁴⁻⁶

The deviations of S-T which occur in clinical cases of infarction conform largely to the experimental findings. Reciprocity in the deviations of S-T is observed not only in the limb leads but often, also, in the leads from the right and left sides of the precordium.* When anteroseptal infarction is present, elevation of S-T in leads from the right side of the precordium may be associated with depression of S-T in leads from the left side (Cases 1 and 2; also in the portion of Fig. 29 dated 1-17-42, of a paper of Wilson and associates).¹ Lead I may then show depression of S-T (Cases 1 and 2), contrary to what is usually expected in anterior wall infarction, and the resulting picture may resemble that which is sometimes associated with lateral wall infarction.⁸ Occasionally, in the presence of anteroseptal infarction, depression of S-T may even be observed in all limb leads; this is shown, for instance, by the case of Wilson and associates,¹ which was cited previously.

*Kisch¹¹ has shown in animal experiments that damage that is strictly limited to one ventricle causes lifting of the S-T segment and of T in homolateral chest leads, and depression of these parts of the tracing in heterolateral chest leads.

Reciprocal deviations of S-T in the chest leads, however, are not seen so often with anteroseptal infarction as might be expected on the basis of the experimental findings. In many cases, elevation of S-T, which is marked in leads from the right side of the precordium where it is associated with deep Q waves, extends as far to the left as Positions C_5 and C_6 (Fig. 7, *B*). This may be due to different factors. First, when anteroseptal infarction is present, the disturbance in blood flow initially may extend far to the left beyond the area which becomes the site of ischemic necrosis, and adequate blood flow in the lateral parts of the anterior wall of the left ventricle may be soon restored by collateral anastomoses. The initial disturbance of blood flow in the lateral area may be responsible for the slight elevation of S-T, which is observed in leads from the left side of the precordium beyond the region which develops characteristic changes of QRS. Second, it must be kept in mind that chest leads, unlike direct leads, tap not only the small area which is covered by the exploring electrode, but a much larger region which may include damaged and undamaged myocardial tissue. The changes of potential thus recorded by a single chest lead may represent a mixture of positive and negative variations. This is even more true of the limb leads. The resulting deviation of S-T recorded in the electrocardiogram depends on whether the positive or negative charge prevails. Hence, in many instances of anteroseptal infarction, elevation of S-T is observed not only in leads from the right side of the precordium but also, though to a less marked degree, in leads from left-side positions. In such instances, when the reciprocal negative potential change of S-T is marked in the posterior (diaphragmatic) wall, a striking S-T pattern is observed in the limb leads. In Lead I there is usually slight elevation of S-T which may be well within normal limits; this is in striking contrast to marked depression of S-T which is seen in Leads II and III (Case 6). The reverse picture may be observed in some instances of posterior wall infarction.

When myocardial infarction is of lateral location, elevation of S-T may be seen in leads from the left side of the precordium, while depression of S-T is noted in leads from right-side positions (Cases 3 and 4; also in a portion of Fig. 36 dated 3-11-42, in a paper by Wilson and associates¹). In the subacute stage of lateral infarction, another reciprocal change is often seen,¹ namely, marked increase in the amplitude of R and T in chest leads from right-side positions (Case 3).

Elevation of S-T in leads from the left side of the precordium in the presence of lateral infarction is not an invariable finding. Wood and associates⁸ have described depression of S-T in Leads I and IV as characteristic of lateral wall infarction. We have observed similar features in some of our cases. Depression of S-T may be due to the fact that the infarction does not extend to the superficial muscle layers (Case 5), or lateral infarction may be located close to the base of the heart so that the usual leads from the left side of the chest do not tap the area of injury, but tap undamaged parts of the myocardium. This apparently happened in some of the cases of high lateral infarction recently published by Wilson and associates,⁹ which showed depression of S-T in leads from the left of the precordium (Figs. 1, 3, and 4).

Depression of S-T in limb and chest leads is sometimes observed in cases of anterior wall infarction prior to the development of the typical electrocardiographic pattern which shows upward displacement of the S-T segment. In such instances depression of S-T, according to Wolferth and associates,⁷ reflects a state of partial deprivation of blood supply prior to complete occlusion. Injury then probably is confined to subendocardial muscle portions. Fig. 7, A, of our Case 7 presents an unusual combination of signs of incomplete and complete occlusion. There is depression of S-T in limb and chest leads. This corresponds to a history of premonitory pain which preceded for two weeks the severe coronary attack. Depression of S-T is accompanied by unusually high T waves, such as are often observed in the earliest stage of coronary occlusion and which are equivalent to elevation of S-T, indicating injury of the subepicardial muscle layers.¹⁰ In a tracing taken eighteen hours after the onset of the coronary attack (Fig. 7, B), depression of S-T is replaced by elevation, and the characteristic QRS changes of anterior wall infarction make their appearance.

SUMMARY

Reciprocal deviations of S-T in chest leads from right- and left-side positions occur in clinical cases of anterior wall infarction. They conform to changes observed in experimentally produced ischemia of the heart muscle.

When myocardial infarction is of anteroseptal location, elevation of S-T in leads from the right side of the precordium may be accompanied by depression of S-T in chest leads from the left side. Then Lead I may also show depression of S-T, and the resulting features may resemble those sometimes seen in the presence of lateral wall infarction.

When myocardial infarction is of lateral location, elevation of S-T in leads from the left side of the precordium may be associated with depression of S-T in leads from the right side. However, when infarction fails to include the superficial muscle layers, or when it is located close to the base of the heart, depression instead of elevation of S-T may be present in leads from the left side of the precordium at the customary level.

There is great variability in the deviations of S-T in limb and chest leads in clinical cases of myocardial infarction. One determining factor is the site and extension of infarction. Another important factor is that the chest leads, unlike direct leads used in the experimental animal, record changes of potential from a far greater area than that covered by an electrode placed directly upon the myocardium, that is, from an area which may include damaged and undamaged myocardium. Thus, positive and negative changes of potential may be mixed and the resultant deviation of S-T will depend on whether the positive or negative potential variation prevails. Therefore, reciprocal deviations of S-T in the chest leads are not invariably observed with anteroseptal or lateral wall infarction. Also, in limb leads, in the presence of anterior wall infarction, elevation of S-T may be inconspicuous in Lead I while marked depression of S-T is noted in Leads II and III. On the other hand, in infarction of posterior site, positive and negative changes in S-T potential which originate in damaged and

undamaged parts of the posterior wall may neutralize each other. Thus, Lead III may show no deviation of S-T, while marked depression of S-T is present in Lead I.

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SPINAL NERVE ROOT PAIN (RADICULITIS) SIMULATING CORONARY OCCLUSION: A COMMON SYNDROME

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THE purpose of this report is to call attention to the syndrome of dorsal spine radiculitis with acute attacks of anterior chest pain, simulating and often mistaken for coronary artery disease.

In most instances, angina pectoris does not present a diagnostic problem. The relation of the chest pain to effort is generally constant from the onset of the illness, and the attacks can be precipitated fairly regularly by exercise tolerance tests under standard conditions. Likewise, in coronary thrombosis with infarction, the clinical picture and electrocardiographic changes leave little doubt in the vast majority of cases. In contrast to this, coronary disease is often first manifested by attacks of prolonged substernal or precordial pain without relation to effort or subsequent evidence of infarction. An accurate diagnosis is very important, for such attacks are frequently followed by coronary occlusion or sudden death.

Every internist and general practitioner will recall cases in which the clinical picture was apparently coronary disease, but where such a diagnosis left questions and doubts. Several years ago, I was able to establish a convincing diagnosis of radiculitis in a few cases of this kind and this led me at least to consider the possibility in similar situations. As a result, the syndrome was found to be surprisingly common.

The following case reports are ten of a group of fifty-six patients under observation during the year 1946 for this condition. It will be noted that these patients had chest pain characteristic of coronary disease. It occurred in the form of attacks, often confined to the substernal or precordial regions. The pain was frequently severe, prolonged, and described as a pressure sensation, a heaviness, a viselike constriction, or an expanding discomfort. It often radiated to the left upper extremity and, at times, to the neck, where it was felt as a choking sensation. Occasionally, it radiated to the jaw, and in a few instances severe attacks were accompanied by pallor and excessive perspiring. Several patients also complained of a peculiar respiratory distress.

But, in addition to the symptoms suggesting coronary disease, other characteristics of the radicular syndrome were often present: attacks occurred (1) in bed at night; (2) after certain movements of the spine, such as bending, turn-

ing from side to side, or getting out of bed; and (3) after such acts as coughing, sneezing, or straining at stool. It was also associated with other postures such as prolonged sitting and relieved when these postures were altered. These facts were most often not volunteered; the patient had to be questioned carefully with this in mind, and sometimes significant information was obtained only after the circumstances of subsequent attacks were observed.

Even when the cardinal characteristics of this syndrome were present, and they were not present in every case, the diagnosis was based on additional data. The most important, diagnostically, was the reproduction of attacks by the application of pressure over the dorsal vertebrae. Such attacks, although short in duration, could be reproduced in many patients with recently acute symptoms and the induced pain had the location, distribution, and character of the spontaneous attacks. Other signs, such as poor posture, spasm of the posterior cervical muscles, and tenderness in the region of the costochondral junctions of ribs and sternum, were present in many patients. Finally, the diagnosis was confirmed in some by the striking response to therapy consisting of postural correction, bed boards, exercises, and, particularly, manipulation and traction of the cervicodorsal spine.

CASE 1.—W. C., a 51-year-old male executive, was seen in consultation the evening of Nov. 29, 1944, for what appeared to be an attack of coronary thrombosis. Earlier that day, while sitting in his office, he developed severe chest pain located substernally and just to the left of the sternum, where it was most intense. It was viselike in character and did not radiate. He felt as though "a weight was compressing his chest." The pain persisted for two and one-half hours before he obtained appreciable relief. His associate noted he was "white as a sheet," and that he perspired profusely. He was helped home, seen by his physician, and given morphine. Later, he recalled that while resting in a chair during the attack, he could relieve the pain somewhat by bending a little forward. After getting into bed, he noted that lying on his left side regularly increased the severity of the pain.

Three weeks before this attack, he had first begun to have pain of a similar character, but milder and of shorter duration. It usually started in the lower axillary region on both sides, squeezed him as in a vise, then localized in the substernal area. He had had approximately twelve attacks of this kind, lasting from thirty to ninety minutes, and in the last few days they had become more frequent and severe. They were not precipitated by walking, but once started, exertion definitely aggravated the pain. Two or three attacks awakened him from sleep, but most of them occurred during the day, most often when in a sitting position. His past history was irrelevant.

Physical examination several hours after the onset of his recent attack found him sitting up in bed, anxious but not uncomfortable. He still complained of mild substernal distress. The heart was not enlarged by percussion. Action was slow and regular. There were no significant murmurs. Lung bases were clear. Blood pressure was 170/110. Routine examination of the spine showed a moderate dorsal kyphosis. Pressure over the seventh cervical and first and second dorsal vertebrae produced marked local tenderness and agonizing substernal pain of the character and distribution noted in the attack described. He was unmistakably angry and annoyed by the procedure. Even light pressure produced viselike pain and substernal distress.

An electrocardiogram taken later was within normal limits, except for slight left axis deviation. X-rays of the cervical and dorsal spines showed the changes of advanced osteoarthritis, with narrowing of the intervertebral foramina of the third and fourth dorsal vertebrae. Orthopedic treatment was advised and, when seen six months later, he stated that severe attacks had not recurred and that mild pain was present on only three occasions.

CASE 2.—F. W., a 64-year-old dentist, was first examined Jan. 13, 1945. He gave a history of two attacks of prolonged substernal pain. The first, five years before, was accompanied by weakness and persisted for several hours. The second, two months before, was similar, and apparently was associated with a slight fall in blood pressure. A diagnosis of coronary thrombosis was made on each occasion. Three electrocardiograms, however, taken within a few weeks after the second attack were, to the patient's knowledge, within normal limits. His past history was unimportant except for frequent attacks of gout over a period of fifteen years.

Physical examination showed large, gouty tophi on both ear lobes. The heart was not enlarged. Sounds were slow and regular. There was a slight systolic murmur over the midsternum. Lungs were clear. Blood pressure was 175/110. There was moderate to marked kyphosis of the upper dorsal spine. An electrocardiogram showed slightly diminished voltage of the QRS complexes in the first three leads, and slight elevation of the S-T interval in Lead CR₄.

Two months later, he complained of pain in the region of the dorsal spine, radiating to both sides of his chest and worse at night. It was relieved by keeping his spine erect and his shoulders back, and aggravated by bending forward. There was exquisite tenderness over the tenth dorsal vertebra, and light pressure reproduced similar pain with radiation as far as the anterior axillary line on each side. Blood pressure was 160/90. He was put on full doses of colchicine, and advised to put boards under his mattress. X-ray of the cervical and dorsal spines showed the changes of advanced hypertrophic arthritis.

He returned nine days later, complaining of an attack of severe anterior chest pain the night before while sitting in a theater. It began in the dorsal region of the back and radiated around to the anterior chest where it was felt as a squeezing pressure pain. He immediately recognized it as the kind of distress he had experienced five years before. It was more severe than his previous attacks, and morphine was necessary for relief. Examination of the heart was not remarkable. Moderate pressure with the thumb over the sixth and seventh dorsal vertebrae precipitated severe pain that radiated from this point around the chest wall to the substernal region. This, he maintained, was exactly what he had had five years before. The pain was elicited with difficulty when he stood very erect or hyperextended his cervicodorsal spine.

The response to orthopedic treatment was prompt, and during the next year chest pain did not recur.

CASE 3.—M. F., a 51-year-old retail store owner, was first seen on March 3, 1943, for an evaluation of his cardiac condition. Five years before, he developed severe substernal pain one evening in the course of walking home in a snow storm. It forced him to stop, and he was apparently relieved by resting. Ten minutes later, a second attack forced him to stop. This time the pain radiated to the left arm. Shortly after getting into bed that evening, he developed severe pain that persisted for fifteen minutes. The pain had the character of a "cramp" and, with it, there was a breathing difficulty described as an inability to breathe or to take a deep breath. He sat up straight in bed and found that this position gave some relief. A few days later, a well-known cardiologist made a diagnosis of serious coronary disease. An electrocardiogram was normal.

Further history revealed short attacks of substernal distress of a similar character on stooping or bending forward over a period of fifteen years. These had become progressively worse during the three years preceding the diagnosis of heart disease. The pain, also described as a "crampy" feeling, occasionally radiated to the left arm and was always quickly relieved by standing up straight. He had had similar attacks in the course of walking and after prolonged sitting, as in playing cards. Physical examination and an electrocardiogram were normal. Blood pressure was 130/80.

During the following winter months he had two attacks of substernal tightening during long walks that followed large meals. These were immediately relieved by stopping. Questioning now brought out the fact that when he stopped, he immediately "straightened up" and threw his shoulders back. He attributed the relief obtained to this act rather than to rest, and maintained that the attacks in the course of walking just prior to the diagnosis of coronary disease were also relieved in this same manner.

Bed boards were recommended and many months later he reported that "cramplike" anterior chest pain occurred occasionally on stooping, but less frequently than prior to the use of bed boards. Now, eight years after the diagnosis of heart disease, physical examination and an electrocardiogram have remained normal. X-rays of the cervical and dorsal spines show the changes of advanced hypertrophic arthritis.

CASE 4.—C. E., a 50-year-old man, was first seen Dec. 7, 1939, for an attack of what appeared to be coronary thrombosis. He was awakened the night before by agonizing substernal pain that persisted for several hours and was relieved only by repeated injections of morphine. Examination of the heart and an electrocardiogram were normal, and during the next few days there was no rise in temperature or leucocytosis. His spine was not examined. He was kept in bed and treated for coronary disease. I saw him on two other occasions during the next few months because of epigastric distress unrelated to eating, but apparently relieved by soda. X-rays of his gastrointestinal tract and gallbladder were negative.

Six years later, while sitting at a meeting, he developed a second attack of excruciating substernal and precordial pain. It was accompanied by marked weakness, nausea, and profuse perspiration. As he was helped to a nearby physician, his symptoms became worse and he vomited several times. A diagnosis of coronary thrombosis was made; morphine was administered. This only dulled his pain which continued throughout that evening and the following night. In bed, the pain was aggravated by moving about. His own family physician saw him that evening and the next morning, and he considered the diagnosis of coronary thrombosis to be unquestioned. His blood pressure had fallen slightly from 125/80 the evening before to 100/70 the next morning. His temperature was slightly elevated.

When I saw him he had just been to the bathroom, and, when questioned, said that his chest pain was less marked while out of bed than it had been during the night. He was lying on his side, his face distorted with pain. Examination of his heart and lungs was normal. When we offered to help him sit up, he refused, saying he had had a bad back for thirty years and could do it with less discomfort himself. Rotation of the head on the neck was restricted on both sides. The dorsal spine, from the second to the eighth vertebrae, was extremely sensitive to light touch. Slight pressure caused him to wince. When moderate pressure was applied over the region of the third and fourth dorsal vertebrae, he suddenly slumped forward in a state of near-collapse. When questioned a little later, he complained of severe pain in the region of the precordium and the suprasternal notch, and begged not to have it repeated. As he sat slumped forward, motionless and faint, he also complained of nausea. After resting a few minutes, the procedure was repeated with lighter pressure, and also caused referred pain to the neck and precordium. There was marked tenderness in the region of the costochondral junctions of the third and fourth ribs anteriorly. An electrocardiogram taken later that day was normal.

With the question of heart disease eliminated, he refused orthopedic treatment. Eight months later, he reported no recurrence of severe attacks although fully active.

CASE 5.—L. B., a 54-year-old housewife, was first seen March 19, 1946, complaining of attacks of severe substernal and anterior left chest pain of three years' duration. They occurred most often at night, forcing her to sit up or walk about. The pain usually started in the mid-dorsal region of the chest posteriorly, moved around the left breast and up under the sternum, causing substernal pressure and a choking or lump sensation in the neck. Less frequently, it started in the substernal region and radiated to both jaws, where it was felt as a numbness as well as pain. She often exclaimed, "My face feels paralyzed!" At times there was radiation down the left arm to the elbow. During attacks there was marked hyperesthesia over the precordium and she often held up her left breast to avoid its pressure against the chest wall. Coughing or sneezing caused a burning pain across the base of her neck. Attacks often lasted one hour, occasionally several hours. They were less frequent during the day and usually occurred when in a sitting or bent-over position. Walking about or straightening up regularly gave relief. On three or four occasions in the past two years, she had attacks in the course of walking fast or climbing stairs; these were relieved by stopping. She averaged three severe attacks a week. There was no dyspnea on exertion. During the past three years, she had been seen by several internists who thought her pain was of cardiac origin.

Physical examination of the heart showed no enlargement. The heart sounds were slow, regular, and of good quality. There was a slight systolic murmur at the apex. The blood pressure was 180/100. The electrocardiogram was within normal limits. A seven-foot roentgenogram showed slight enlargement of the left ventricle.

Examination of the spine showed a markedly increased dorsal curve. Motion of the neck was restricted in all directions. Coughing caused pain at the base of the neck. Slight pressure over the second and fourth dorsal spinous processes produced exquisite pain in the substernal region similar to that experienced in previous attacks. It was immediately felt in the midsternal region, under the left breast, in the throat region, and along the left jaw as high as the temporomandibular joint. Substernally, it felt like a constriction. Slight pounding over the second or third dorsal vertebrae produced a sharp pain which stabbed from the back straight through to the sternum and from there up to the neck, the left jaw, and frontoparietal aspect of the head.

She was referred to an orthopedist. He noted that hyperextension of the dorsal spine at the level of the sixth dorsal vertebra caused radicular pain referred to the left costal margin. Following traction and hyperextension exercises, there was dramatic improvement.

CASE 6.—J. B., a 37-year-old business executive, was first seen April 1, 1946. He had had approximately eight attacks of severe, sharp anterior left chest pain during the past year, unrelated to effort or meals, and usually lasting but a few minutes. Two or three attacks occurred during sleep. The morning of the day of examination he was awakened by an "agonizing" attack. The pain was sharp, localized below the left nipple, and persisted for fifteen minutes with varying intensity. During the attack he did not move and was unable to take a deep breath. He felt he was suffocating, and at moments his breathing became rapid and gasping. Automatically, he assumed a slightly bent-forward position, his left shoulder drawn down toward the left chest. This gave some relief. There was no substernal pain, no radiation to the extremities. This attack was more severe than previous ones, and the first to alarm him. On driving to the office, he noted that laughing provoked the same pain.

Physical examination of the heart was normal. There was muscle spasm in the left cervical area, and rotation of the neck was markedly restricted to the right. Pressure over the seventh cervical spinous process regularly precipitated pain, localized to a small area just within the left nipple. With it there was respiratory distress. These symptoms were of the character described in his severe attack.

An electrocardiogram with standard chest leads was entirely within normal limits. X-ray examination of the cervicodorsal spine showed hypertrophic changes, straightening of the cervical spine, slightly increased dorsal kyphosis, narrowing of the interspaces, and scoliosis to the left in the dorsal region.

Orthopedic treatment quickly relieved his acute condition. During the past nine months there has been no recurrence.

CASE 7.—I. B., a 36-year-old man, was seen on April 20, 1946, complaining of severe substernal and left chest pain of five weeks' duration. The pain started in the lower interscapular region and radiated to the midsternum and precordium. It often awoke him at night and was present in the morning just after getting out of bed. Recently, however, instead of wearing off in the morning, as before, it recurred intermittently during the day. The night attacks had also become more pronounced. Pain was brought on or aggravated by bending, prolonged sitting, taking deep breaths, coughing, or excessive talking.

A week before, he had a severe attack after lifting a rubbish barrel. It started as a "cramp" between his shoulder blades which "settled out" in the anterior midchest region and persisted for ten minutes. Two days later, it recurred with greater severity while out walking. He was unable to continue. After some time he slowly made his way back to the office. His secretary told him he looked pale and very sick. He was unable to breathe and felt his "wind was cut off." He noted he was gasping for breath. This respiratory disturbance and mild substernal pain continued intermittently for four or five hours.

Physical examination showed no cardiac enlargement, slow regular sounds, and no murmurs. Blood pressure was 130/90. There was marked spasm of the posterior cervical muscles with limitation of head rotation bilaterally and a moderate kyphosis of the upper dorsal spine. Firm

pressure with the thumb over the seventh and eighth dorsal vertebrae caused local tenderness and reproduced substernal and precordial distress of the character noted in his spontaneous attack. With the application of pressure and the onset of chest pain, his breathing became rapid and shallow; and he complained, "It knocks the wind out of me." An electrocardiogram with standard chest leads was within normal limits.

The response to orthopedic treatment consisting of manipulation and traction was dramatic, and after the first week of treatment there was a complete disappearance of symptoms which have not recurred up to now, nine months later.

CASE 8.—E. T., a 42-year-old housewife, was seen April 20, 1946, complaining of attacks of severe sharp pain in the region of the left breast and "shortness of breath" of three months' duration. Her family physician thought she had serious coronary disease. The pain started under the breast, and most often radiated to the left shoulder and inner side of the left arm. She had had approximately twelve attacks in this period, varying in duration from ten to fifteen minutes. Most occurred when she was lying in bed. Three or four occurred in the course of walking and forced her to stop. Bending forward gave definite relief on each occasion. She volunteered that walking, especially with bundles, precipitated attacks. During most of these attacks, her breathing became shallow; she "didn't dare take a deep breath." Coughing, sneezing, and sighing did not precipitate or aggravate the pain.

Physical examination of the heart was not remarkable. There was no enlargement. At the apex there was a slight, localized systolic murmur. The lungs were clear. There was tenderness and muscle spasm in the left cervical area and marked limitation of neck rotation to the right. Moderate pressure over the sixth to eighth dorsal spinous processes produced acute pain three or four cm. to the left of the sternum in the fifth and sixth intercostal spaces. As she winced with pain, she panted and said, "My breath is cut off." The chest pain and dyspnea were of the same character as that noted in the spontaneous attacks. An electrocardiogram with standard chest leads was normal.

This patient refused orthopedic treatment. Her family physician, six months latter, stated she still has recurring attacks, although less frequently.

CASE 9.—C. C., a 63-year-old ship-model builder, was seen May 18, 1946, complaining of upper substernal pain and respiratory difficulty of two weeks' duration. He described it as a squeezing, pulling, and at times gnawing sensation that was also felt a little to the right of the sternum. At times it persisted for hours. It was precipitated or aggravated by certain types of physical exertion, particularly after eating, but did not occur in the course of walking. Associated with it was an inability to take a deep breath and "fill out my lungs." Three days before, while digging in the garden, as he stooped to lift out a bush he was seized by a severe "gripping" upper substernal pain. He was forced to sit down, unable to move. After twenty minutes, the pain subsided, but it did not entirely disappear.

Three months before, while lying in bed on his right side, he tried to turn over and was seized by the same gripping pain. It felt as though somebody was "pulling the insides out of me." Changing back to his original position, the pain subsided. He had had approximately fifteen such attacks during the past month. He also experienced mild pain in the left arm on awakening in the morning, and midsternal and precordial distress when weeding in the garden.

Physical examination showed a tall man with a narrow chest. The heart was normal. The liver was felt two fingers' breadth below the costal margin with deep inspiration. Blood pressure was 130/70. An electrocardiogram was normal. During the examination, he developed upper substernal pain. Hyperextension of the spine immediately relieved it. When the natural kyphotic position was again resumed, the pain recurred. Hyperextension again gave relief. There was no local tenderness nor referred pain after firm pressure over the dorsal vertebrae.

He was seen again ten days later because of an attack of the same respiratory distress, unassociated with chest pain, following prolonged sitting. The lungs were clear.

While attacks were not reproduced in this patient by pressure over the dorsal spine, the characteristic history and the unmistakable relief obtained by hyperextension during a spontaneous attack established the diagnosis.

CASE 10.—B. R., a 50-year-old housewife, was first seen Aug. 23, 1946, complaining of "shortness of breath" and attacks of severe chest pain of two years' duration. She had been under observation for marked hypertension for several years, and five years before, had an attack of prolonged left chest pain. This was considered to be of coronary origin by a well-known cardiologist, and her attacks during the past two years were ascribed to the same condition. Most of them occurred at night, and were often associated with respiratory distress. The pain was described as a dull ache. It usually started posteriorly along the inner aspect of the scapula and radiated anteriorly to the neck and around the left breast, localizing over a small area within the left nipple line. The attacks usually lasted ten or fifteen minutes. Soon after the onset she was "unable to breathe" and could not take a deep breath. At times she gasped in an effort to obtain more air. At the start of each attack, she sat straight up in bed, arched her shoulders back, and at times exercised her arms to obtain relief. She belched a great deal and this usually led to hiccough, which continued for a few minutes until the pain subsided. She had had a few attacks in the course of walking and climbing hills.

During the past two years she was constantly troubled by posterior neck pain and occipital headache. She also had mild substernal pain on getting out of bed in the morning. She complained of being "stiff all over," and regularly took a hot bath each morning to relieve her joint symptoms.

Physical examination showed marked limitations of neck rotation to the left. The heart was slightly enlarged by percussion. The first sound was accentuated, and there was a slight systolic murmur at the apex, a moderately loud systolic at the base, and an early aortic diastolic murmur along the left border of the sternum. Blood pressure was 240/120. The lung bases were clear. There was slight scoliosis of the dorsal spine to the left with slight angulation at the level of the fourth dorsal vertebra. To the left of this region there was muscle spasm, and pressure at this point of angulation produced wincing pain anteriorly in the region of the third left rib and parasternal line. A similar, but less severe, pain was produced by light pounding with the fist over the second to seventh dorsal vertebrae. With the onset of pain in each instance, respiration became rapid, shallow, and gasping. An electrocardiogram showed no deviation from the normal. X-rays of the cervical and dorsal spines showed hypertrophic arthritis.

She was later seen by an orthopedist who noted, in addition to the preceding, a slight limp, a pelvic tilt with the right iliac crest higher than the left, scoliosis in the lumbar area to the right with compensatory scoliosis in the dorsal spine to the left, producing slight angulation at the level of the fourth vertebra. The left lower extremity was three-fourths of an inch shorter than the right. Orthopedic treatment consisting of heel lift on the left foot, bed boards, cervical traction and manipulation, and moist heat gave immediate partial relief. After a few weeks of treatment, pain was almost completely abolished. At the time of writing, seven months later, she is active with only mild discomfort on rare occasions.

DISCUSSION

The literature on dorsal spine radiculitis is meager. In 1927, Phillips¹ called attention to the importance of examining the spine in the presence of thoracic and abdominal pain and showed that pain of this origin could be mistaken for angina pectoris, gallbladder, and kidney disease. He noted the occurrence of points of tenderness lateral to the sternum and in the axilla. The following year, Gunther² gave a comprehensive description of the dorsal radicular syndrome, and with Kerr³ and Sampson,⁴ he analyzed the symptoms in fifty patients whose chief complaint was chest pain. It was bilateral in most instances, and a common zone was over the heart with radiation to the back and left upper extremity. The onset was mild in their cases, and although pain might appear abruptly, it did not have the crushing or tearing qualities that prevented other activities. They stressed the bothersome, nagging character of the pain, which was ag-

gravated by certain positions and movements of the spine and never severe enough to require opiates. They maintained further that radiation did not occur from the precordium directly to the side of the neck, to the occiput, or to the jaw in any instance and that no autonomic nervous phenomena, such as salivation or sweating, occurred. They were obviously describing the milder form of the syndrome and not the type of case reported here that so strikingly resembles coronary disease.

In 1934, Nachlas⁵ considered the radicular syndrome and presented three case reports, two of which simulated heart disease. One patient who had been kept in bed for severe precordial pain was promptly relieved by traction. Two years later, Hanflig⁶ reported five cases of osteoarthritis of the spine with shoulder girdle pain of radicular origin. One of his patients also had substernal and precordial pain relieved by traction. In 1942, Kelly⁷ summarized the clinical features in forty cases with chronic cervical arthritis. Eight of these had chest pain characterized as pseudoanginal. In the same year, Smith and Kountz⁸ reported four cases with anginoid pain due to spinal deformities and arthritis, and in two of these the pain was described as a substernal oppression. The syndrome was discussed again in 1943 by Hanflig⁹ and by Martin.¹⁰

The occurrence of substernal pain as a result of sensory nerve root irritations is understandable, for the pain in coronary disease and radiculitis are both referred from the skin along the same path. In the former, according to theory, there is an irritable focus in the cord; in the latter, in the nerve root itself. It is, therefore, not surprising that the pain of radiculitis has the location, distribution, and characteristics of true coronary pain. In the cases reported, this pain was often substernal or precordial in location and was most often described as an oppressive, viselike, constricting pain.

The segmental distribution of the spinal nerves has been established and mapped out by various workers, and the roots generally involved in chest pain are the second to seventh dorsal. It will be recalled that when symptoms were reproduced by pressure over a given vertebra in the cases reported, the pain did not necessarily correspond with the segmental distribution of that root. This is explained by the fact that pressure over one region of the spine can exert nerve root irritation at some distance from this region. Pain over the precordium, corresponding to the fourth dorsal root, for example, could be elicited in one patient (Case 10) by pressure at any point from the second to the seventh dorsal vertebrae.

Many of these patients also had marked tenderness in the region of the costochondral junctions, particularly of the second to fifth left ribs. It frequently persisted long after acute symptoms had disappeared spontaneously or after orthopedic treatment. In several instances, it was reduced or temporarily abolished in the course of traction applied to the cervical spine.¹¹ This sign is common in patients with generalized hypertrophic arthritis and joint symptoms of the extremities. It was found in several patients with symptoms of cervical radiculitis who did not have chest pain at that time.

A close relationship between arthritis of the spine and radicular symptoms has been pointed out by several authors.^{2-9, 12-14} Smith and Kountz also stressed

the role of postural defects, and maintained that they were more significant than the roentgenogram findings of osteoarthritis. They called attention to straightening, stiffening, and kyphosis with markedly decreased movement of the spine. Many of the patients reported here also had postural changes and several had an old history of low back syndromes.

In addition to chest pain, many of the patients had symptoms of cervical radiculitis. This is not unexpected, for osteoarthritis of the spine is usually generalized, and a postural strain at one point is not infrequently transmitted to another. Cervical symptoms, therefore, should at least alert us to the possibility of simultaneous involvement of the dorsal roots. Kelly stressed the occurrence of two less commonly appreciated symptoms of this syndrome, namely, suboccipital headache and vertigo. One patient with chest pain also had incapacitating attacks of vertigo that were immediately relieved by manipulation and traction. The presence of cervical symptoms led to a reinvestigation of the chest pain, which subsequently proved to be of radicular origin. Patients with the syndrome frequently have pain and stiffness of the neck, and examination reveals muscle spasm* and tenderness with limitation of motion, particularly on rotation of the head.

During acute attacks, many patients also complained of a peculiar respiratory difficulty characterized as an inability to take a deep breath. With this restriction of respiration, breathing was, at times, rapid and shallow. Inability to take a deep breath is a common symptom of an anxiety neurosis and, particularly when chest pain is atypical, it may easily be mistaken for a psychosomatic complaint. With this in mind, patients presented here were studied carefully and at length to exclude this possibility. In several of the cases reported, the respiratory symptoms were also provoked by pressure over the dorsal spine. Such respiratory symptoms may also occur in attacks as the presenting complaint with little or no chest pain and be mistaken for attacks of cardiac asthma.¹⁵ One patient with repeated attacks suggesting cardiac asthma was seen with Hanflig. Within a few days after traction treatment, these symptoms completely disappeared and have not recurred during the past twelve months. The exact mechanism is unknown. It is probable that, as in cervical radiculitis, the motor roots are also involved, causing muscle spasm and an inhibition of respiration.

Coronary disease and hypertrophic arthritis of the spine with radicular symptoms may coexist in the same patient, for both are common with advancing age. At the present time, I have several patients with angina pectoris, past myocardial infarcts, and congestive heart failure, who in addition have had unmistakable symptoms of cervicodorsal radiculitis. Physicians are familiar with patients followed for angina pectoris, who from time to time, in addition to typical attacks also complain of precordial or substernal distress which is often mild, unrelated to effort, and occasionally lasts for long periods of time. In some, these symptoms are psychosomatic evidence of anxiety. In others, however, they are due to coexisting nerve root irritation. Many patients have suffered a great deal because of a false impression that such pain was due to their

*I am indebted to Dr. George M. Lane for demonstrating muscle spasm in some of these cases.

heart disease. On the other hand, it is most important to be alert for manifestations of coronary disease in all patients under consideration or treatment for radiculitis. This is generally a long illness with acute attacks recurring over a period of years, and the possibility of coronary disease is ever present.

Recognition of dorsal radiculitis is not difficult in most instances if the possibility is at least considered in differential diagnosis. When the chest pain can be reproduced by pressure over the dorsal spine, or by forceful flexion of the head, the diagnosis is established. The cases reported were largely selected because of such findings. Many patients, however, do not show this sign, particularly after the acute phase has subsided. In such patients the history will often reveal many characteristics of radiculitis. When most of the attacks have occurred at night in the reclining position, on bending, or in the course of prolonged sitting, the radicular syndrome should be suspected. When the history is less suggestive, other orthopedic signs may be present, and the diagnosis can be further tested by the therapeutic response.

A more difficult situation is where, in addition to attacks of severe substernal pain, there is also a history of what appears to be atypical angina pectoris. Several patients had chest pain at one time or another in the course of walking. A few of these were forced to slow down or stop and the pain appeared to be relieved by rest. Such attacks seldom occurred exclusively in the course of walking or continuous exertion as in the early stages of angina pectoris. The pain was usually of longer duration, and most often did not cease immediately when the patient rested. Nevertheless, the tendency was to give false value to a history of this kind when major attacks of chest pain simulating coronary disease were under consideration. This was probably responsible for the early mistaken diagnosis in Case 4. The history in this case indicated that the relief obtained after stopping was probably due to the act of hyperextending his spine. This response of "straightening up" and throwing the shoulders back, noted in several histories, was often carried out unconsciously by the patient in search of a more comfortable position. In several instances, relief was immediate and striking and the response was of diagnostic value.

The importance of recognizing this syndrome cannot be overemphasized. The commonness of the syndrome can be judged by the number of cases seen during the year 1946. Most of these patients are thought to have coronary disease, their activities are curtailed, and their lives often handicapped by the fear of an impending attack. It is the author's conviction that the syndrome will be found to be common if its possibility is entertained in differential diagnosis.

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EXTRASYSTOLES IN GROUPS

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TWO beats following each other within a short time and separated from the next identical group by a longer diastole are classified among the arrhythmias which are called bigeminy or coupled beats. This term, coined prior to the electrocardiographic era, includes, however, at least three different disturbances. First, the succession of groups in which each beat of the basic rhythm is followed by a premature contraction; in this instance, the term bigeminy as a synonym for coupled rhythm is generally accepted. A second form includes examples of an arrhythmia which was later recognized with the aid of the electrocardiograph as due to an auriculoventricular block; a 3:2 block, for instance. The third disturbance is a rare condition which Wenckebach named "true bigeminy."^{27,28} In this type, both beats of each group look alike in the electrocardiogram, for they originate in the same focus.

It is the purpose of this communication to describe rare clinical and experimental tracings of this third form, showing groups of extrasystoles separated from other groups by a longer pause.

A-V NODAL TACHYCARDIA IN MAN

We have observed a supraventricular tachycardia with extrasystoles in groups in only one instance; this occurred in a 45-year-old woman, who suffered from a rheumatic mitral lesion and who had almost daily attacks of paroxysmal tachycardia. Carotid sinus pressure easily restored sinus rhythm.

Fig. 1,A shows Lead II obtained during a paroxysm. Groups of two beats are close together and are separated by a longer interval from the preceding or following group. The successive ventricular intervals in Fig. 1,A measure 0.47, 0.35, 0.39, 0.35, 0.47, 0.36, 0.42, 0.35, 0.46, 0.36, 0.40, 0.36, 0.47, 0.35, and 0.41 second. Thus, the difference between the shortest and the longest interval amounts to 0.12 second.

The beginning of Fig. 1,B shows a similar arrhythmia during another attack. The intervals measure 0.38, 0.50, 0.42, 0.54, 0.40, 0.52, and 0.40 second. The registration of the electrocardiogram was interrupted for a few seconds and then started again while carotid pressure was applied. As shown in the second part

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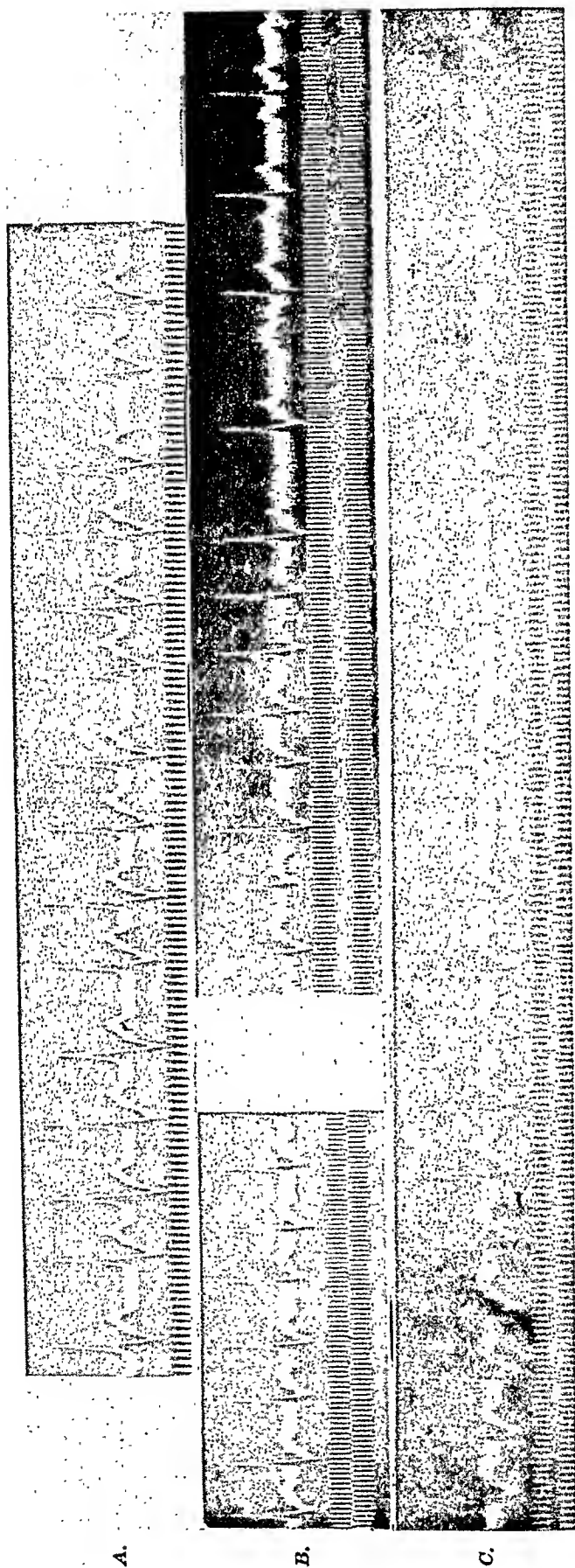


Fig. 1.—A shows groups of two A-V nodal extrasystoles separated by a longer pause. In the beginning of B a similar arrhythmia is present; pressure on the carotid sinus (second part of B) abolishes the A-V extrasystoles, and sinus rhythm reappears. C shows the effect of carotid sinus pressure on an A-V nodal tachycardia without alternation of cycle length (all tracings were taken in Lead II).

of Fig. 1,*B*, carotid pressure stopped the tachycardia immediately. This proves that we are dealing with a paroxysmal tachycardia.

The form of the QRS complexes during the attack differs from that during regular sinus rhythm. This is, in our opinion, not the result of changes which might be anticipated because of the increased rate, since during the arrhythmia the form of the QRS complex following the long and the short diastoles remains the same. P waves were never visible in any lead during the tachycardia, even in the long diastoles. One must assume, therefore, that the broad, short S wave during the tachycardia actually is due to an inverted P wave and that we are dealing with a tachycardia originating in the A-V node.

Fig. 1,*C* shows an electrocardiogram obtained during another attack, which was also abolished by carotid pressure. This time, however, the rhythm was regular. The successive cycles during the attack measure 0.38, 0.40, 0.40, 0.40, 0.38, 0.39, 0.40, 0.40, and 0.40 second. Regular tachycardias and tachycardias with group formation appeared often and in an unpredictable manner.

VENTRICULAR TACHYCARDIA

Clinical Observations.—Fig. 2,*A* shows tracings of Lead III obtained from a patient with a ventricular tachycardia of the type which Gallavardin designated as "extrasystolie a paroxysms tachycardiques." A more detailed description of the clinical features of this case has been reported elsewhere.²² In Fig. 2,*A*, groups of two ventricular extrasystoles showing the same form and separated from other similar groups by a longer pause are clearly visible. Occasionally, simple bigeminy appeared; often during attacks of ventricular tachycardia not only the form but also the rhythm alternated, and, occasionally during the attacks, a regular rhythm was observed without any change in form of the QRS complexes. The successive ventricular intervals in Fig. 2,*A* measure 0.44, 0.49, 0.94, 0.48, 0.92, 0.48, 0.92, 0.48, 0.52, 0.46, 0.87, 0.44, and 0.45 second.

In these groups, which often appeared spontaneously, the long diastole separating each group measured exactly twice the length of the interval between two extrasystoles which were close together. Thus, the possibility of a rapidly working ventricular center with exit block had to be considered, and one was inclined to assume that periodically one stimulus formed by the extrasystolic center was not conducted to the ventricle.

The extrasystoles of this patient were always abolished temporarily by quinine and quinidine. Fig. 2, *B*, *C*, and *D* shows three strips of tracings in Lead III which were obtained immediately after the intravenous injection of 0.4 Gm. of quinine bihydrochloride. Between the tracings *B* and *C*, as well as between *C* and *D*, strips with about twenty contractions are omitted.

The beginning of Fig. 2,*B* shows the tachycardia with alternating forms of ventricular complexes and an alternation of the length of diastole, the usual type of arrhythmia found in this patient during several years of observation. The tachycardia ended suddenly about thirty seconds after the injection (middle of Fig. 2,*B*). One bigeminal group appears with a ventricular extrasystole coupled to a normal sinus beat. From then on groups of two abnormal beats appear,

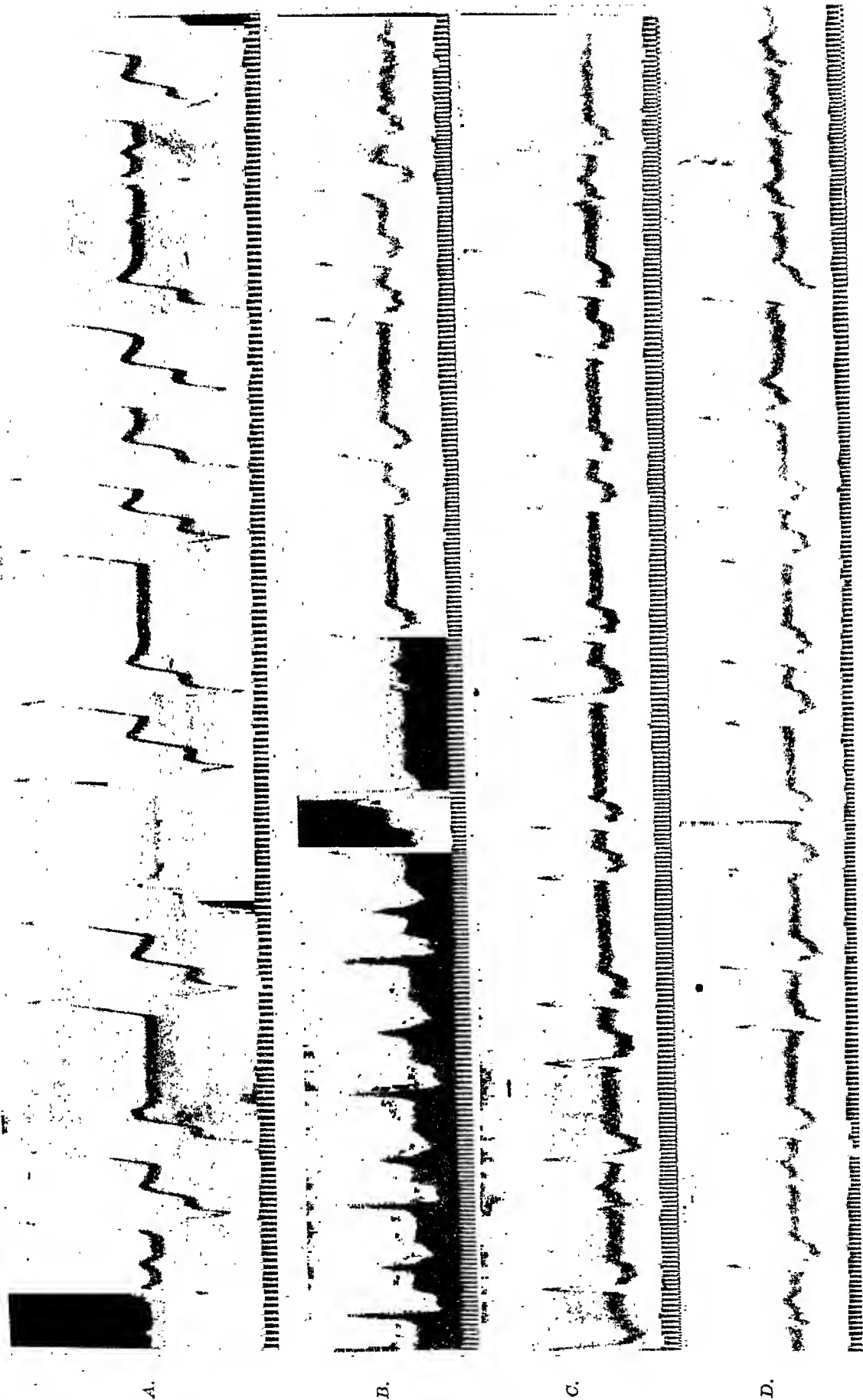


Fig. 2.—A shows groups of two ventricular extrasystoles separated by a longer pause. B, C, and D show the effect of an intravenous injection of quinine on a paroxysmal ventricular tachycardia with alternating form of the QRS-T complexes (all tracings were obtained in Lead III).

separated from each other by a long interval, and only occasionally is a supraventricular beat interposed. The successive diastoles in Fig. 2,*B* measure 0.42, 0.56, 0.42, 0.52, 0.42, 0.56, 0.40, 0.56, 0.42, 0.86, 0.38, 1.04, 0.46, 1.02, 0.44, 0.60, and 0.44 seconds. The intervals in Fig. 2,*C* are 0.44, 0.72, 0.46, 0.80, 0.44, 1.01, 0.46, 1.04, 0.45, 1.08, 0.46, 0.80, 0.44, 0.78, 0.44, and 1.06 seconds.

The same rhythm is registered in Fig. 2,*D* when a sinus rhythm suddenly appeared. The intervals measure 0.44, 0.74, 0.44, 0.82, 0.44, 0.76, 0.46, 0.76, 0.48, 0.76, 0.48, 0.80, 0.85, 0.74, 0.60, and 0.62 second.

Accordingly, in this patient group formation was spontaneous during attacks of ventricular tachycardia and appeared when the administration of quinine changed the rhythm from a ventricular tachycardia to a normal sinus rhythm.

Experimental Observations.—Similar tracings were seen in experiments on dogs and were obtained under a variety of conditions.

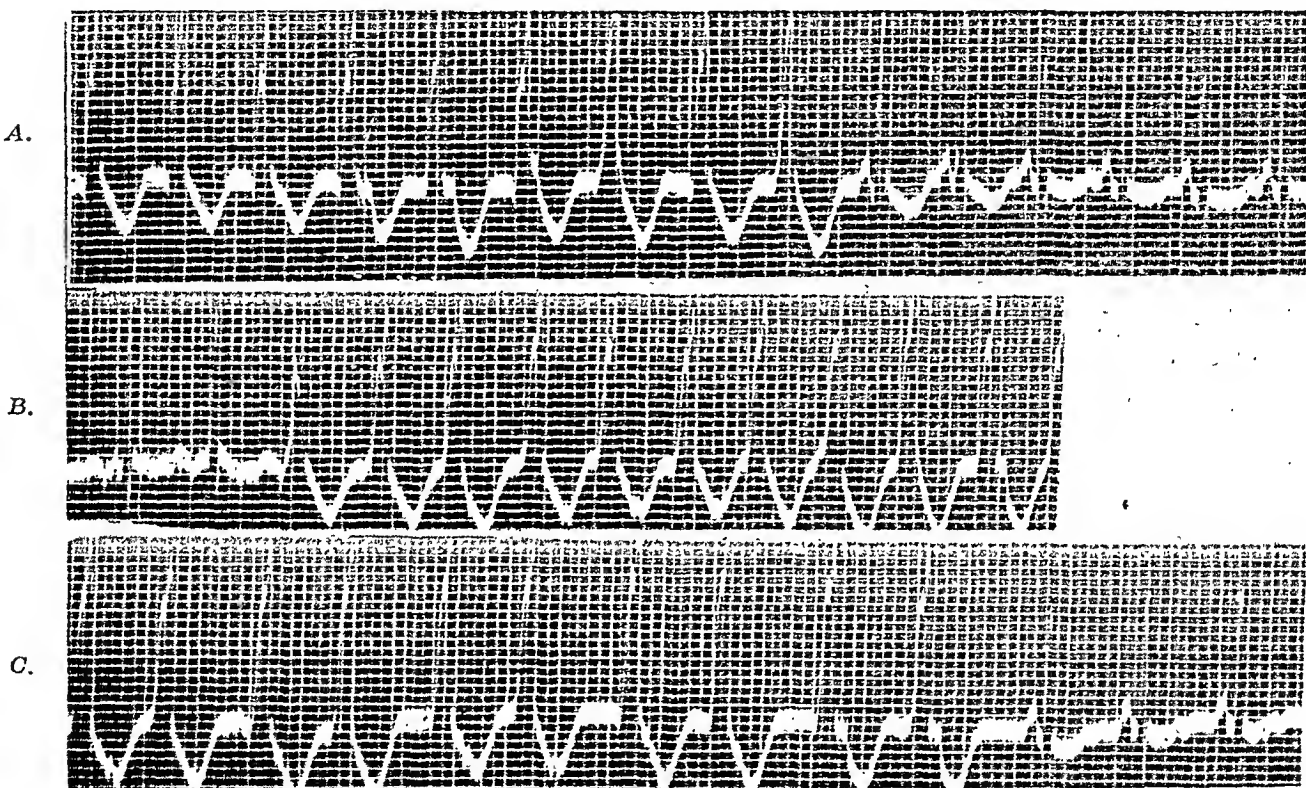


Fig. 3.—Dog experiment, Lead II. *A* shows the end of a paroxysmal ventricular tachycardia caused by application of a 1 per cent solution of barium chloride to the cardiac surface. Stimulation of the right sympathetic nerves of the heart causes the tachycardia to reappear (Fig. 3, *B*); a few seconds later, groups of extrasystoles emerge (Fig. 3, *C*).

Fig. 3 demonstrates the end of a paroxysmal ventricular tachycardia (Lead II) which appeared after brushing a 1 per cent solution of barium chloride on a small area of the conus of the right ventricle. This area was about 3.0 mm. in diameter.¹⁸ The successive diastoles during the tachycardia measure 0.32, 0.32, 0.33, 0.33, 0.32, 0.34, and 0.35 second, a gradual slowing occurring toward the end. The tachycardia is followed by a regular sinus rhythm. Stimulation of the cardiac branches of the right sympathetic nerve by means of a strong

faradic current caused the ventricular tachycardia to reappear at a rate of 180 to 214 beats per minute. The individual diastoles were 0.28 to 0.32 second (Fig. 3,B). About 4.5 seconds later, Fig. 3,C was recorded. In this tracing there are groups of two abnormal beats with alternating length of the diastoles. The intervals in Fig. 3,C, obtained during the tachycardia, measure 0.31, 0.36, 0.33, 0.39, 0.32, 0.40, 0.34, 0.41, and 0.36 second and the greatest difference amounts to 0.1 second.

A similar disturbance was observed during vagus stimulation. Fig. 4,A (Lead II) was registered during another dog experiment in which a 5 per cent solution of barium chloride was brushed on the conus of the right ventricle. Single ventricular extrasystoles appeared and came so late in diastole that they were preceded by normal P waves (beginning of Fig. 4,A). The right vagus in the neck was stimulated with a faradic current at the sixth systole in Fig. 4,A, as indicated on the tracing by a slight slurring produced by the faradic current. With the beginning of this stimulation groups of two or three ventricular extrasystoles appear at once¹⁸ and they are separated by a longer pause. The successive diastoles in Fig. 4,A measure 0.41, 0.51, 0.45, 0.51, 0.50, 0.45, 0.41, 0.62, 0.41, 0.61, 0.44, 0.41, 0.60, 0.46, and 0.40 second. In Fig. 4,B, a continuation of Fig. 4,A, the diastoles have the following lengths: 0.44, 0.42, 0.60, 0.49, 0.42, 0.56, 0.44, 0.42, 0.60, 0.46, 0.40, 0.55, and 0.42 second. The end of the vagus stimulation is marked by the disappearance of the alternating current approximately in the middle of Fig. 4,B. The extrasystoles soon vanished and regular sinus rhythm followed.

Similar arrhythmias appeared occasionally without stimulation of the cardiac nerves when a solution or a few crystals of barium chloride were applied to the cardiac surface, or when the solution was injected subepicardially. A regular tachycardia always follows the application of sodium chloride solutions¹⁸ whereas solutions of barium chloride, digitalis, or strophanthin²¹ often lead to irregular tachycardias and the formation of groups. Similar irregular tachycardias follow an intravenous injection of barium salts.

Fig. 5,A shows the electrocardiogram before, and Fig. 5,B, after the application of a 5 per cent solution of barium chloride to the apex of the right ventricle near the anterior coronary sulcus. The extrasystoles appeared after a latent period of eight minutes. Group formation with longer pauses between the groups is clearly visible. The successive diastoles in Fig. 5,B have the following lengths: 0.43, 0.48, 0.61, 0.45, 0.46, 0.53, 0.56, 0.64, 0.47, and 0.49 second.

About twelve minutes later, the extrasystoles disappeared. Faradic stimulation of the cardiac branches of the left sympathetic nerve caused at first a sinus tachycardia and, after this subsided, a series of extrasystoles appeared with fixed coupling (Fig. 5,C), originating in the same focus as the abnormal beats of Fig. 5,B. Suddenly, groups of two extrasystoles reappeared, separated by a longer pause. The last five cycles in Fig. 5,C measure: 0.42, 0.52, 0.46, 0.73, and 0.46 second.

Finally, similar groups were produced by warming the focus of origin of the extrasystoles by a thermode. Fig. 6 shows an electrocardiogram which was

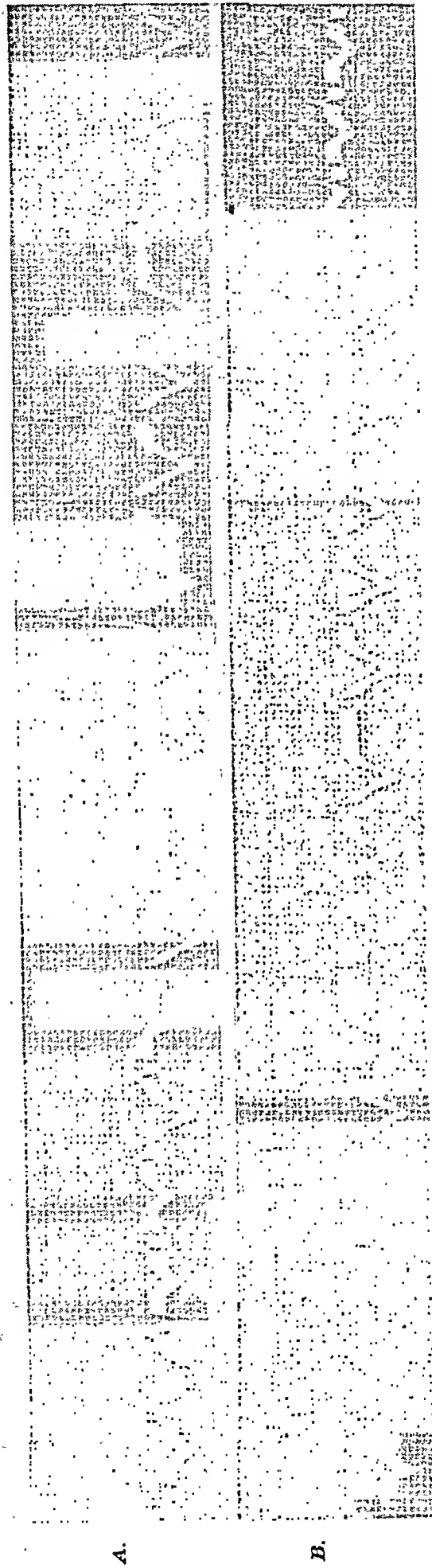
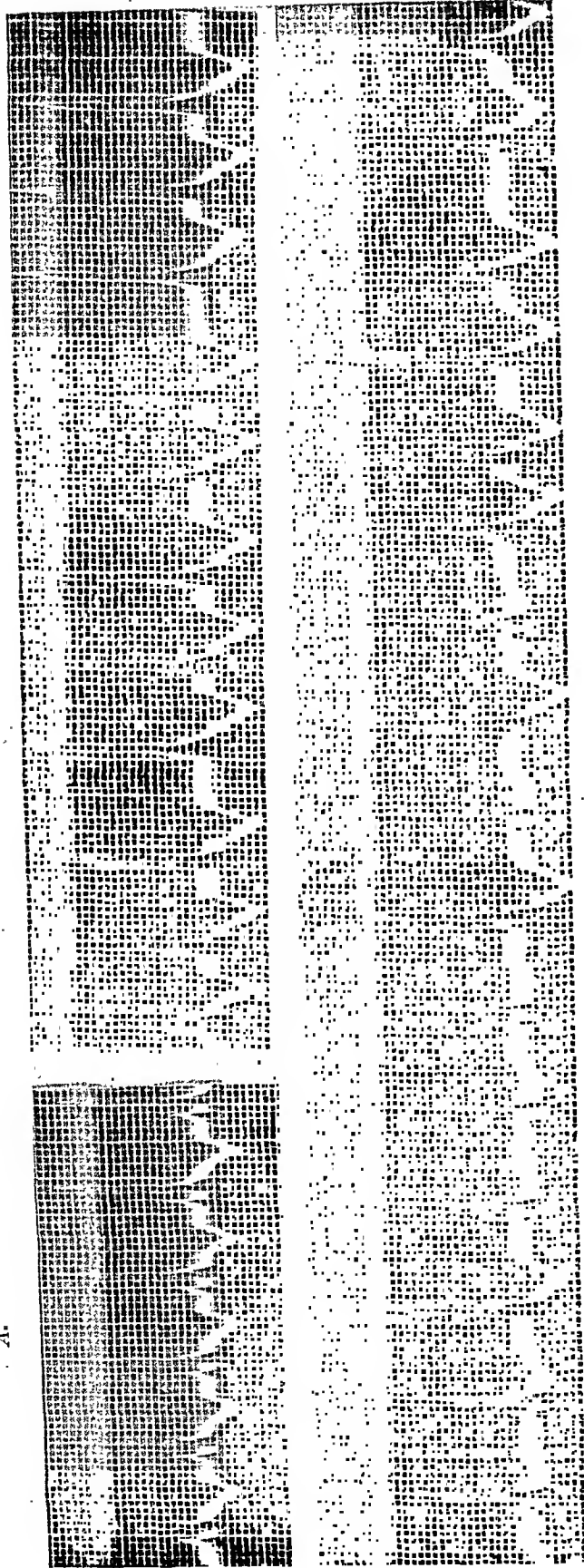


Fig. 4.—This tracing shows the appearance of groups of two or three ventricular extrasystoles during stimulation of the right vagus. Dog experiment. Lead II; a 5 per cent solution of barium chloride was applied to the right ventricle earlier.

A.



C.

Fig. 5.—A shows the electrocardiogram before, B, after, the application of a 5 per cent solution of barium chloride to the cardiac surface. C was obtained after faradic stimulation of the left cardiac sympathetic nerves. Dog experiment, Lead II.

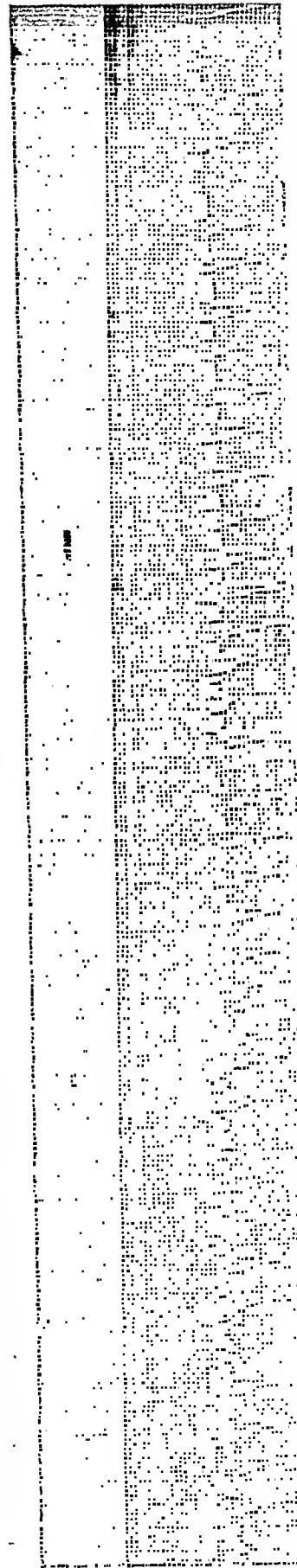


Fig. 6.—Dog experiment, Lead II. Series of four ventricular extrasystoles follow each normal beat at the beginning of the tracing. Warming of the site of origin of the extrasystoles (the short black horizontal lines represent signals) increases the number of the extrasystoles and leads to alternation of cycle length.

registered in an experiment in which 0.05 c.c. of Strophosid* was injected sub-epicardially on the conus of the right ventricle. Each normal beat was followed for a time by four extrasystoles. Warming of the area of injection with strict avoidance of mechanical irritation led to an acceleration of rate and an increase of the number of the extrasystoles. The beginning and the end of the warming period is indicated by the short horizontal black lines in Fig. 6. After the warming was stopped, the extrasystoles persisted for a few seconds and again groups of two extrasystoles, separated by a longer interval, are present. The successive diastoles in the last third of Fig. 6 measure 0.32, 0.34, 0.37, 0.31, 0.39, 0.31, 0.38, 0.32, 0.39, 0.32, 0.38, 0.31, and 0.38 second.

In this way groups of two or three extrasystoles formed after the application of barium chloride to the cardiac surface with and without vagus or sympathetic stimulation. The same disturbance of rhythm appeared on warming the focus of origin of strophanthin extrasystoles.

DISCUSSION

When bifid pulse curves were observed in experimental and clinical tracings, the term "pulsus bigeminus" was applied because it was correctly assumed that these pulses were due to a rapid succession of two systoles, followed by a longer pause.^{24,25} The underlying cardiac action was called bigeminy, and for many years the phenomenon was not sharply separated from alternating pulse. When it was discovered that the intermittent pulse is, in most instances, caused by premature contractions or extrasystoles, pulsus bigeminus was explained by the appearance of extrasystoles following every beat of the basic rhythm.

Some authors, however, insisted that pulsus bigeminus was created by a different mechanism and had no relationship to extrasystoles.^{5,27} These authors did not regard the term bigeminy as applicable to a disturbance in which some beats were due to normal systoles and others to extrasystoles, caused by a presumably different mechanism and originating in a different part of the heart. It was proposed to reserve the term bigeminy or "true" bigeminy exclusively for cases²⁷ in which both beats were formed in the same way and originated in the same focus.

Lewis agreed that a bigeminy with both beats having the same form in the electrocardiogram represented an arrhythmia of a totally different character than the usual bigeminy of coupled rhythm. But he called the term "true bigeminy" premature, since the evidence for irregular stimulus formation in one locality was insufficient at that time.¹² His proposal to use the term "bigeminy" only in the sense of coupling was almost generally accepted.^{†13}

The term "true bigeminy" probably will not become popular because it arose out of the controversy just discussed. "Twin contraction" is merely a translation of bigeminy and this term, like that of "paired extrasystoles," is not

*Sandoz Chemical Works, Inc., New York, N. Y.

†Before the use of the electrocardiograph, a true bigeminy was differentiated from extrasystoles by the absence of a compensatory pause. Subsequently, it was shown that most instances originally described as true bigeminy were actually the result of a complete auriculoventricular block with extrasystoles.

applicable because sometimes more than two abnormal beats follow each other directly (Fig. 3). Therefore, "extrasystoles in groups" seems to us to be the best designation for the present.

Several years ago, we occasionally saw in the experimental animal tracings of this kind. In a dog who received barium chloride intravenously in doses too small to cause any disturbance of rhythm, warming of a small area of the ventricular surface with a thermode evoked extrasystoles in groups of two. Both beats of each pair looked identical and were separated from each other by a diastole of 0.30 second, while the pause between each group measured 0.47 second.²⁰ A similar disturbance was observed after the administration of aconitine.¹⁹ Here again aconitine, per se, did not cause any change in the electrocardiogram. During faradic vagus stimulation, however, groups of two extrasystoles having the same form appeared. The single extrasystoles were separated by a diastole of 0.24 second, while the long pause between the groups averaged 0.64 second.

Clinically, similar changes in the length of the diastole were observed, especially during a paroxysm of auricular tachycardia. These cases were described as examples of alternation of the length of diastole, since a short pause was regularly followed by a long one. In a study on the constancy of rhythm during attacks of paroxysmal tachycardias, made under the direction of one of us, MacKinnon¹⁶ described the two patients from whom Figs. 1 and 2 were obtained. The tracing of one case (Fig. 1) at that time was wrongly interpreted as showing a paroxysmal auricular tachycardia. Being interested only in the presence of an arrhythmia during the tachycardia, the alternation of cycle length was not stressed nor discussed.

In a series of eight unselected cases of paroxysmal auricular tachycardia, differences of the interventricular interval of 0.0358 second only were found with an occasional slight tendency to alternation.⁶ Definite alternation of cycle length in the auricle in a case of paroxysmal auricular tachycardia was reported by Katz,¹¹ and during auricular flutter by Wilson.²⁹ The alternation of cycle length during paroxysmal auricular tachycardia was the subject of a special study by Barker, Johnston, and Wilson.² This phenomenon was found in ten out of 100 unselected cases of paroxysmal auricular tachycardia. The differences in cycle length reached in some instances almost 0.1 second.

Occasionally, the first beat following an extrasystole shows the same form as the extrasystole. This was seen at first by Lewis in auricular extrasystoles.¹⁴ If this abnormal beat after the postextrasystolic pause is followed by an extrasystole of the same form, the disturbance shown in Fig. 2 appears. This phenomenon has been observed repeatedly in ventricular extrasystoles,^{3,4,13,19} particularly during the administration of digitalis. It was also registered during complete auriculoventricular block.²²

The mechanism underlying the appearance of groups of extrasystoles represents an unsolved problem. When encountered during a tachycardia, the possibility of a circus movement alternately using a path of different length has been stressed.² If found with a slower cardiac activity and isoelectric pauses between single groups, another mechanism must be present. The question

arises whether both beats are formed in the same manner or whether they are due to different types of stimulus formation. The separation of an automatic stimulus formation (such as the normal sinus rhythm, some A-V rhythms, or an idioventricular rhythm) from abnormal heterogenetic rhythms (such as extrasystoles) has been abandoned by Lewis,¹⁵ but is, in our opinion, necessary. Automatic stimuli are formed "by themselves" while there is no doubt that an extrasystole with fixed coupling is related to and caused by the preceding beat.

It is possible that under certain conditions two or more discharges take place in a center, as seen occasionally in a nerve¹⁰ or muscle fiber.^{1,17} Multiple response to a constant stimulus is possible.⁹ Double discharges, bigeminy, have been registered from the so-called Purkinje fibers under a variety of conditions.^{8,26} Grouped discharges, "each group made up of two or more impulses closely spaced," were seen in skeletal muscle fibers.¹

Another interpretation of these tracings might be based on the assumption that a rapid regular stimulus formation takes place. One of the stimuli is periodically blocked, so that a longer pause results. In this case the pause caused by the blocked beat could measure double the period between the beats, which are close together. It could, however, be shorter, if one assumes that one of the extrasystoles formed in the center is conducted rapidly to the chamber in which the center is situated, another one is conducted with some delay, and the third one is blocked. We would have a 3:2 block after the manner of a Wenckebach period. This possibility has been considered repeatedly.^{2,20}

With a very rapid stimulus formation, such as is encountered in flutter, an alternation of the length of the auriculoventricular interval has been observed repeatedly in clinical tracings.⁷ During electric stimulation of the auricles of the dog, with high rates, alternation of intra-auricular conduction has appeared.¹⁵

Barker, Johnston, and Wilson are inclined to favor a circus movement as the cause of auricular paroxysmal tachycardia, and base their position largely upon the occurrence of an alternation of cycle length. The authors know "of no published examples of alternation in cycle length, which have been clearly shown to depend solely upon the discharge of impulses by a single center." The appearance of extrasystoles in groups following the topical administration of barium salts (Fig. 5) and of a regular alternation of cycle length on warming the point of origin of strophanthin extrasystoles (Fig. 6) speaks against a circus movement as the cause of alternation in the tracings reproduced and shows that an irregular discharge of stimuli in a center, or a regular stimulus formation with irregular conduction, must be responsible. The latter possibility and a circus movement are improbable in those tracings in which the single groups are separated by very long pauses (Fig. 2).

Our present knowledge of these arrhythmias and of the physiology of stimulus formation does not permit one to decide whether the underlying mechanism is always the same. It is even uncertain whether the alternation of cycle length during a tachycardia has the same mechanism as the same phenomenon when the heart is slow.

SUMMARY

Instances of alternation of cycle length during an A-V nodal tachycardia and during a paroxysmal ventricular tachycardia in man are described. In the latter case a similar phenomenon was observed during the change from the tachycardia to sinus rhythm following an intravenous injection of quinine.

Application of barium chloride or strophanthin to small areas of the cardiac surface of the dog also causes groups of extrasystoles separated by longer pauses. These arrhythmias were often elicited during vagus and following sympathetic stimulation in these experiments. Finally, the phenomenon was observed during warming of the site of origin of extrasystoles produced by subepicardial injection of strophanthin.

Similar observations in the literature are discussed. The different mechanisms which may lead to this disturbance of rhythm are reviewed. Irregular stimulus formation in a center is probable; regular stimulus formation with a disturbance of conduction from the center to the rest of the heart is possible only in some of these tracings.

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THE USE OF DICUMAROL IN EXPERIMENTAL CORONARY OCCLUSION

I. THE INEFFECTIVENESS OF DICUMAROL WHEN LIGATION IS THE METHOD OF OCCLUSION

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UNTIL recently the treatment of acute coronary thrombosis has been directed generally toward the control of its symptoms or to the prevention or control of its complications. By and large it has not been concerned with the underlying pathologic process. However, the successful use of anticoagulant therapy in certain other thrombotic or thromboembolic disease states during the last few years has stimulated¹ the trial of a similar approach to the treatment of acute coronary thrombosis. In the three clinical reports thus far available, the results seemed encouraging. In the first report, Nichol and Page, Jr.,² described an 18 per cent mortality in fifty attacks of coronary thrombosis seen in forty-four unselected private patients treated with Dicumarol. All of the twenty-six patients who were treated in their first attack survived. No mural thrombi nor systemic or pulmonary emboli were found in six autopsied cases. In only one patient was there clinical evidence of pulmonary embolism and this patient had not received an optimal dose of Dicumarol. In the second study,³ a comparison of fifty dicumarolized patients with sixty nondicumarolized patients revealed a reduction of embolic phenomena to one-eighth and of mortality rate to one-fifth in the former group. In the third investigation, Wright⁴ found an 11 per cent mortality among forty-three patients treated with Dicumarol. He considered this group to have an expected mortality of 60 to 70 per cent from such complications as propagation of coronary artery thrombi, formation of multiple thrombi, or dissemination of peripheral emboli. Wright also found a 12 per cent mortality rate among thirty-three patients in their first or second uncomplicated attack of coronary thrombosis, in whom he estimated the anticipated death rate as 20 to 30 per cent, but hesitated to conclude that Dicumarol was effective in this group.

The only experimental study of this subject is that of Solandt and Best⁵ who found that preliminary heparinization of dogs in large part prevented the artificial

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production of thrombi in the left coronary artery, as well as the resultant infarct, following the introduction of sodium ricinoleate into the lumen of a section of the artery and its retention there for a few minutes. The clinical limitations of this approach were conceded. We are aware of no experimental investigation of the effect of anticoagulant therapy upon coronary thrombosis and myocardial infarction once these conditions have been induced.* It seemed worthwhile, therefore, to determine the effect upon experimental coronary artery occlusion of anticoagulant therapy begun after the thrombotic process had already been initiated. This method offered the opportunity to study not only the survival rate of treated, as compared with untreated, animals, but also the effect of treatment upon the evolution of the electrocardiographic changes and the gross and microscopic changes in the heart.

METHODS

Experiments were done on forty healthy dogs of both sexes. The dogs were anesthetized with intravenous Nembutal (30 mg. per kilogram of body weight). The dogs were placed on the left side, the chest shaved, and an electrocardiogram was taken of the three limb leads and one apical precordial lead paired with the left limb lead. A rubber endotracheal tube was introduced to prevent insufflation of air after the thorax was opened. The left side of the chest was opened aseptically, and five to six inches of the fifth rib were resected. Care was taken to obtain good hemostasis with fine silk ligatures. The lung was packed away with a moistened gauze pack and the ribs spread with a self-retaining retractor. The pericardium was opened longitudinally. A point on the descending branch of the left coronary artery approximately 3.0 cm. from the orifice of the left coronary artery was selected. The exact points of the ligations are given in Tables I and II. The epicardium was incised and a segment of the descending branch teased free by blunt dissection; the freed vessel was ligated with a fine silk ligature. On rare occasions, the vein accompanying the descending branch had to be ligated as well as the artery.

At first, attempts were made to produce thrombosis by crushing the artery. In most instances the vessel was observed to be occluded during the operative procedure. However, the electrocardiographic changes in these animals were minimal and subsequent pathologic studies showed, with two exceptions, normal myocardium and patent coronary arteries. In the later experiments ligation was used exclusively.

The pericardium was left open. The chest wall was closed with interrupted linen sutures to the pleura and deep muscles, and interrupted silk sutures were used for the superficial muscles and skin. No dressing was applied to any of the wounds. An electrocardiogram was taken immediately postoperatively. If anticoagulant therapy was to be used, Dicumarol, 5.0 mg. per kilogram of body

*Since this paper was written, Blumgart, H. L., Freedberg, A. S., Zoll, P. M., and Lewis, H. D., reported on "The Effects of Dicumarol in Experimental Acute Coronary Occlusion" before the New England Heart Association on Feb. 24, 1947. Their method was somewhat different but their conclusions were substantially the same as those reported here.

weight, was given by gavage while the animal was still anesthetized. Subsequent daily doses were given in capsules in meat.*

The prothrombin time was determined daily in the animals receiving Dicumarol. An attempt was made to keep the prothrombin time between 10 and 30 per cent of the prothrombin time of a normal dog. If the prothrombin time was between 10 and 30 per cent, 0 to 2.5 mg. per kilogram of body weight were given, depending upon the history of that animal's response to Dicumarol. If the prothrombin time was over 30 per cent, 2.5 to 5.0 mg. per kilogram of body weight were given.

The same difficulty was experienced in keeping the prothrombin times in the optimum 10 to 30 per cent range that was found in human patients. To err on the radical side, the dogs were kept below a 10 per cent prothrombin time, rather than over 30 per cent. Most of the dogs had prothrombin times under 30 per cent on the second postoperative day. Due to the use of Dicumarol immediately following operation, and perhaps in part due to the relatively large doses, hemorrhage was occasionally troublesome. Of nineteen dogs, only six had prothrombin times over 35 per cent of normal after the first forty-eight hours. Of these six dogs, only three had more than one determination above 35 per cent.

The prothrombin times were determined on venous blood with Maltine thromboplastin, employing a modification of Quick's method and using a thromboplastin suspension.⁶⁻⁸ A determination was run on each dog in 100 per cent plasma and in 20 per cent plasma. Normal, untreated dogs were used as controls. The normal prothrombin time in 100 per cent plasma was about seven seconds. The values were expressed in per cent of normal, the percentages being taken from a chart which had been plotted from actual dilutions of plasma from which all prothrombin was removed by repeated Seitz filtering.

Electrocardiograms were taken daily for the first week postoperatively and also on the fourteenth postoperative day just before the animal was autopsied. Following operation, the animals were active in their cages. They received the standard planned ration of food used in the animal farm.

RESULTS

Group I comprised five dogs which were used as controls and did not receive Dicumarol (see Table I). The descending branch of the left coronary artery was crushed.

One animal died forty-five minutes following operation. The left coronary artery in this animal was crushed 1.5 cm. from its point of origin. It was considered that the point of occlusion was too high to be compatible with survival. Subsequent crush and ligation experiments were therefore done at lower levels. A second dog which had developed no electrocardiographic changes died during the night of the fourth postoperative day, and no infarct was found. The three remaining dogs showed minimal or nonspecific electrocardiographic changes, such as T-wave reversal or ventricular premature beats. One dog had an infarct

*The Dicumarol was a preparation manufactured by Eli Lilly and Company, Indianapolis, Indiana, and marked as Dicumarol, Pulvules 271.

measuring 2.0 x 0.3 x 1.5 cm. on the left anterior side of the septum with the typical histologic changes seen in myocardial infarction. Another dog had persistent slight elevation of RS-T₄ and slight depression of RS-T₂ and RS-T₃. Examination of the heart in this dog showed no areas of infarction. The third animal had nonspecific electrocardiographic changes (T-wave reversal, ventricular premature beats) and small focal areas of infarction were found in the heart.

In short, one of the five animals should be excluded, because it did not live long enough for the purpose of the experiment. This leaves four animals which can be considered as satisfactory from the point of view of the experiment. One animal showed neither electrocardiographic nor pathologic changes. Of three animals showing electrocardiographic changes, two developed myocardial infarcts and one did not.

TABLE I. EXPERIMENTAL CRUSHING OF DESCENDING BRANCH LEFT CORONARY ARTERY

EXPERIMENT	COURSE	DISTANCE OF LESION FROM CORONARY ORIFICE (CM.)	ELECTROCARDIOGRAPHIC CHANGES	HEART
<i>Group I. Dogs Receiving No Dicumarol</i>				
1	Died 4 days P. O.	2.5	None	No infarct
2	Died 45 min. P. O.	1.5	None	No gross abnormality
3	Autopsy 14 days	3.5	Persistent slight elevation RS-T ₄ and depression RS-T ₂ and ₃	No infarct
4	Autopsy 14 days	2.9	VPB, T-wave reversal	Infarct
6	Autopsy 14 days	4.3	VPB, reversal T ₁ , ₂ , and ₃	Infarct
<i>Group II. Dogs Receiving Dicumarol</i>				
5	Died 1 day P. O. (hemorrhage)	3.9	None	No infarct
7	Autopsy 14 days	2.8	Slight elevation RS-T ₂ and ₃ , normal by 6th day	No infarct
9	Died 13 days P. O. (empyema)	2.9	Transient reversal T ₂ and ₃	No infarct
11	Autopsy 14 days	2.6	None	No infarct
12	Autopsy 14 days	3.2	Slight elevation RS-T ₂ and ₃ , normal by 6th day	No infarct
14	Autopsy 14 days	No lesion found	Slight depression RS-T ₂ and ₃ , normal 1 day P. O., 1st degree heart block; normal 14 days P.O.	No infarct

Key to abbreviations: VPB—ventricular premature beats.
P.O.—postoperatively.

Group II. was made up of six animals which received Dicumarol after the descending branch of the left coronary artery was crushed (see Table I). One animal died of hemorrhage the day following operation and showed neither electrocardiographic changes nor myocardial infarction. One animal did not

TABLE II. EXPERIMENTAL LIGATION OF DESCENDING BRANCH OF LEFT CORONARY ARTERY

EXPERI- MENT	COURSE	DISTANCE OF LESION FROM CORONARY ORIFICE (CM.)	ELECTROCARDIOGRAPHIC CHANGES	HEART
<i>Group III. Dogs Receiving No Dicumarol</i>				
16	Autopsy 14 days	2.5	Slight depression RS-T ₂ and ₃ , slight elevation RS-T ₄ ; RS-T ₂ and ₃ normal on 14th day, RS-T ₄ still elevated	No infarct
17	Died during operation	3.2	Ventricular fibrillation	No gross abnormality
18	Died during operation	—	Ventricular fibrillation	No gross abnormality
19	Autopsy 14 days	—	Elevation RS-T ₄ and de- pression RS-T ₂ and ₃ ; VPB singly and in runs; normal 9 days P.O.	Infarct
20	Autopsy 14 days	3.0	RS-T displacement, normal 3 days P.O. VPB disap- pearing by 4 days P.O.	Infarct
21	Autopsy 14 days	2.7	Persistent RS-T displace- ment, reversal T ₁₋₃ . VPB and APB	Infarct
22	Autopsy 14 days	3.6	Persistent RS-T displace- ment, S-A block, T ₂ and ₃ reversal and APB disappearing by 5 days P.O.	Infarct
23	Autopsy 14 days	3.2	Depression RS-T ₂ , normal 14 days P.O. 1st degree A-V block, normal 7 days P.O.; S-A block normal 14 days P.O. Persistent T-wave reversal	Infarct
24	Autopsy 14 days	3.5	T-wave reversal and VPB, normal by 7 days P.O.	Infarct
27	Died during operation	3.5	Ventricular fibrillation	No gross abnormality
30	Died during operation	2.5	Ventricular fibrillation	Traumatic hemorrhage
32	Died during operation	2.8	No electrocardiogram. Probably ventricular fibrillation	No gross abnormality
35	Autopsy 14 days	5.0	Elevation RS-T ₁ and ₄ , elevation RS-T ₂ and ₃ with "late inversion" normal 4 days P.O., T-wave reversal normal 4 days P.O.	No infarct
36	Autopsy 14 days	6.5	Elevation RS-T ₄ with "late inversion" and T-wave reversal; VPB singly and in salvos; all normal 4 days P.O.	Infarct

TABLE II. EXPERIMENTAL LIGATION OF DESCENDING BRANCH OF LEFT CORONARY ARTERY—(CONT'D)

EXPERIMENT	COURSE	DISTANCE OF LESION FROM CORONARY ORIFICE (CM.)	ELECTROCARDIOGRAPHIC CHANGES	HEART
<i>Group IV. Dogs Receiving Dicumarol</i>				
8	Autopsy 14 days	2.8	Elevation RS-T ₂ and ₃ and S-A block, normal 14 days P.O. Ventricular tachycardia, normal 3 days P.O.	Infarct
10	Autopsy 14 days	2.8 (Not ramus descendens)	Persistent elevation RS-T ₄ and depression RS-T ₂ . VPB and ventricular tachycardia, normal 3 days P.O.	No infarct
13	Autopsy 14 days	3.4	Elevation RS-T ₄ and depression RS-T ₂ and ₃ , normal 7 days P.O. VPB and ventricular tachycardia, normal 3 days P.O.	Infarct
15	Died 4 days P.O. (hemothorax)	4.0	Elevation slight RS-T ₁ , slight depression RS-T ₂ and ₃ , still present 4 days P.O., VPB disappearing 4 days P.O.	Infarct
25	Autopsy 14 days	3.7	RS-T displacement, normal 14 days P.O.; VPB normal 4 days P.O.	Infarct
26	Autopsy 14 days	2.3	Persistent elevation RS-T ₁ and ₄ , and depression RS-T ₂ . VPB normal 4 days P.O.	Infarct
28	Autopsy 14 days	3.1	Elevation RS-T ₁ , depression RS-T ₂ and ₃ , normal 14 days P.O. VPB, normal 4 days P.O.	No infarct
29	Autopsy 14 days	3.4	RS-T displacement. No electrocardiogram after 7th day	Infarct
31	Died 7 days P.O.	3.5	Depression RS-T _{1,2} and ₃ , normal 4 days P.O.	Infarct
33	Autopsy 14 days	4.2	Depression RS-T ₂ and ₃ , normal 7 days P.O. VPB normal 2 days P.O.	Infarct
34	Died 4 days P.O.	Too decomposed to examine	Elevation RS-T ₁ and ₄ with "late inversion" and VPB, still present 3 days P.O.	Too decomposed to examine
37	Died 8 days P.O.	3.8	Elevation RS-T ₄ , depression RS-T ₂ and ₃ , still present 6 days P.O.; APB and VPB normal 4 days P.O.; paroxysmal ventricular tachycardia, normal 2 days P.O.; A-V block normal 4 days P.O.	Infarct

TABLE II. EXPERIMENTAL LIGATION OF DESCENDING BRANCH OF LEFT CORONARY ARTERY—(CONT'D)

EXPERIMENT	COURSE	DISTANCE OF LESION FROM CORONARY ORIFICE (CM.)	ELECTROCARDIOGRAPHIC CHANGES	HEART
38	Died 8 days P.O.	4.0	RS-T displacement still present 7 days P.O.; VPB normal 4 days P.O.	Infarct
39	Died 4 days P.O.	Too decomposed to examine	Elevation RS-T ₁ , depression RS-T ₂ , VPB and ventricular tachycardia still present 2 days P.O.	Too decomposed to examine
40	Died 7 days P.O.	3.4	RS-T displacement still present 5 days P.O.; VPB normal 4 days P.O.	Infarct

Key to abbreviations: RS-T elev. (used indiscriminately)—elevation RS-T₁ and ₄ and depression RS-T₂ and RS-T₃.

VPB—ventricular premature beats.

APB—auricular premature beats.

S-A block—sinoauricular block.

A-V block—auriculoventricular block.

P.O.—postoperatively.

develop electrocardiographic changes during the fourteen day period of observation. One dog showed reversal of T₂ and T₃ and two showed minor and transient RS-T segment displacements. The sixth dog had transient RS-T displacement and first degree heart block. The hearts of none of these animals were infarcted.

In brief, one animal died the day following operation and should be excluded. None of the five remaining animals developed myocardial infarction, and four of the five showed minor electrocardiographic changes.

Group III consisted of fourteen animals. These were control animals and received no Dicumarol. In each animal the descending branch of the left coronary artery was ligated (see Table II). Five animals died of ventricular fibrillation during the operation.

Eight animals showed RS-T segment displacement, which was persistent during the fourteen day period of observation in two dogs and transient in six. In addition, five of these had transient ventricular premature beats occurring either singly or in short runs. Two developed transient auricular premature beats. Two showed sinoauricular block and one, first degree auriculoventricular block. Transient T-wave reversal and ventricular premature beats were noted in the ninth dog. Definite infarcts were found in all but two of these animals.

In summary, five of the fourteen animals died during operation and must be discarded. Myocardial infarction was present in seven animals and absent in two animals. Eight animals, including both of those which did not have a myocardial infarct, had moderately severe to severe electrocardiographic changes.

Group IV comprised fifteen dogs who received Dicumarol. In thirteen dogs the descending branch of the left coronary artery was ligated (see Table II). In two animals autopsy showed that a coronary branch other than the descend-

ing branch was ligated. Both showed changes in the electrocardiogram, and one had a myocardial infarct. However, since the criteria for the experiment were not fulfilled, these animals were discarded. Three animals died four days postoperatively, one of hemorrhage and cardiac infarction and one of infarction alone. Two died eight days postoperatively, one with infarction and the other of infarction and hemorrhage. Eight animals were sacrificed following the usual fourteen day period of observation.

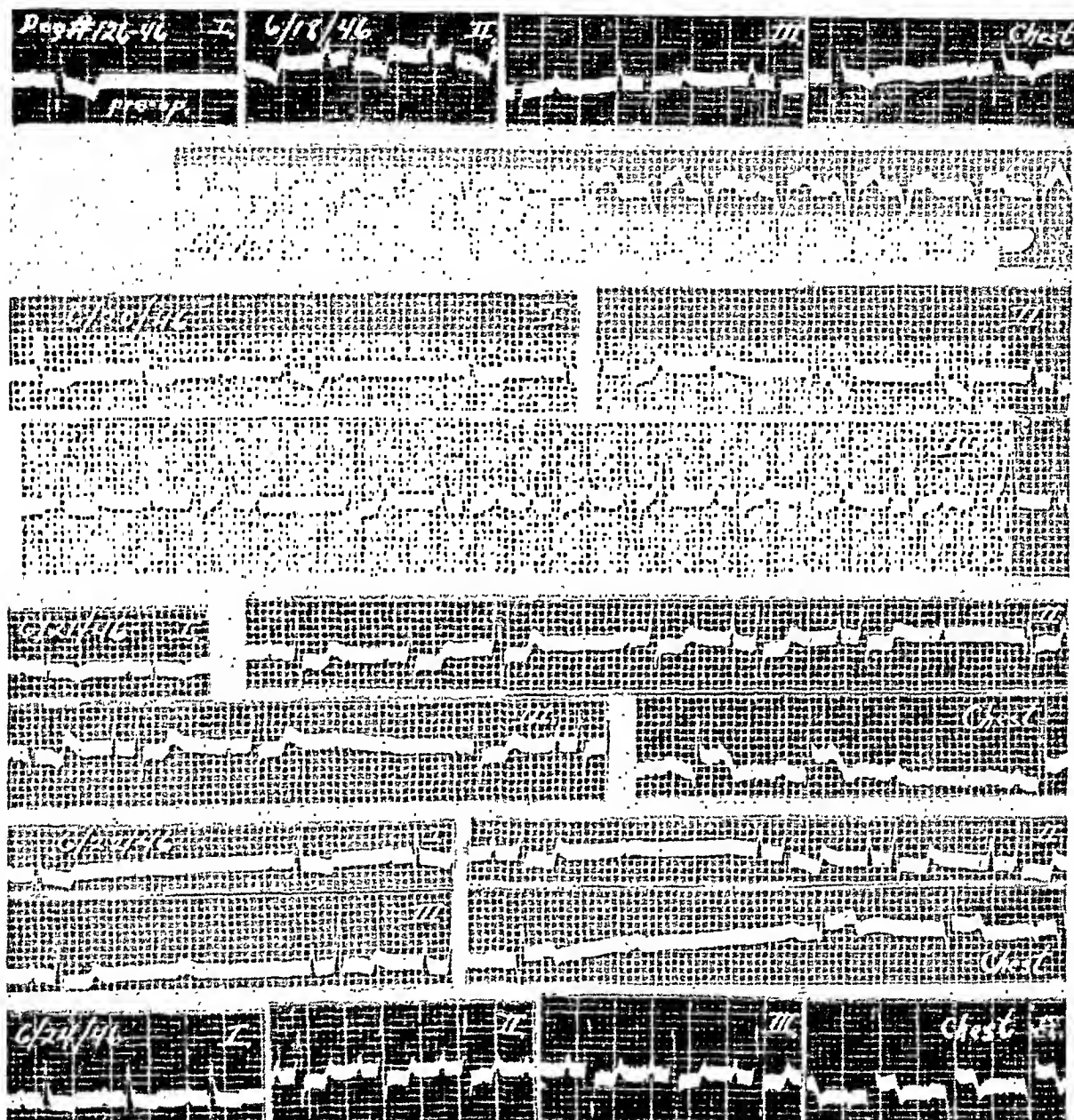


Fig. 1.—Dog 37. Ligation of descending branch of left coronary artery 3.8 cm. from origin of left coronary artery, June 18, 1946. Dicumarolized. Prothrombin content 14 per cent of normal, June 22, 1946. Tracing taken day after operation shows paroxysmal ventricular tachycardia. On June 20, 1946, complete heart block is associated with ectopic ventricular (escape) beats. On June 21, a similar mechanism is associated with a premature nodal beat showing aberrant ventricular conduction (Lead II) and RS-T segment elevation in the chest lead. On June 22, second degree heart block is noted. On June 24, normal rhythm is re-established, but RS-T deviations are still present. Dog sacrificed on fourteenth postoperative day. Post-mortem examination showed a full-thickness anterior wall infarct measuring 15 by 40 millimeters.

Five of the fifteen dogs showed transient, and one showed persistent, RS-T segment displacement. The seven animals who died before the completion of the fourteen day observation period showed RS-T segment displacement which was still present at the time of death. In one animal the RS-T segment was still displaced on the seventh day, but no tracings were taken after this date. Ten

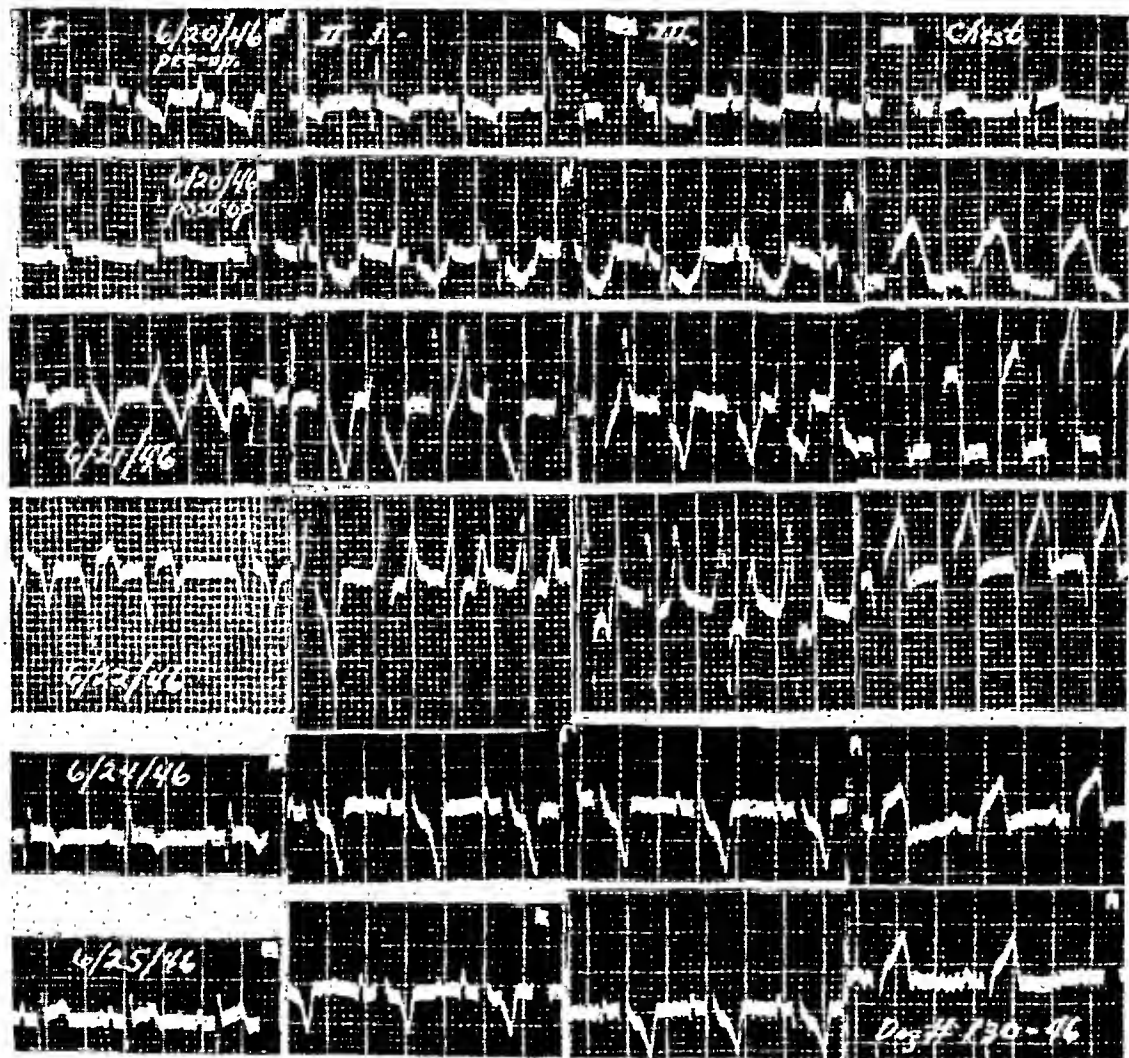


Fig. 2.—Dog 40. Ligation of descending branch of left coronary artery 3.4 cm. from origin of left coronary artery, June 20, 1946. Dicumarolized. Prothrombin content 14 per cent of normal on June 23. Tracings taken postoperatively on the day of operation show elevation of RS-T in Lead I and in the chest lead, and depression of RS-T in Leads II and III. On June 21, premature ventricular beats occur, singly or in salvos, while the chest lead shows monophasic action currents. Premature ventricular beats are still present on June 22, but the rhythm is again regular on June 24. Slight elevation of RS-T in Lead I and in the chest lead, and depression of RS-T in Lead III, are still present in the last recorded tracing on June 25. The animal died eight days postoperatively. Post-mortem examination showed a full-thickness anterior wall infarct measuring 20 by 20 millimeters.

dogs showed transient ventricular premature beats; one, transient auricular premature beats; three, ventricular tachycardia; one, sinoauricular block; and one, complete followed by second degree heart block; all of these changes were restricted to the first five or six days of electrocardiographic observation.

The hearts of two of the dogs which died on the fourth postoperative day were too decomposed to examine. One heart showed no infarcts in spite of having shown electrocardiographic changes diagnostic of myocardial infarction. All of the remaining ten hearts were infarcted.

In summary, two of the fifteen dogs were discarded because of improper placement of the ligature, two hearts were too decomposed to examine for infarcts, and ten of the eleven hearts examined showed infarction. All thirteen animals followed by the electrocardiograph showed moderate to marked changes characteristic of coronary occlusion.

DISCUSSION

A comparison of the control and treated groups in which the coronary artery was crushed showed no striking differences in the electrocardiographic and pathologic changes observed. These groups were too small and the results obtained by the method used too inconsistent to warrant further comment.

Comparison of the control and treated groups in which the descending branch of the left coronary artery was ligated showed similar electrocardiographic and pathologic findings. Infarction was found in seven of nine control animals and in ten of eleven treated animals. Electrocardiographic changes of approximately equal severity were found in nine control animals and in thirteen treated animals. It should be noted that seven of the dogs surviving operation and receiving Dicumarol died during the eight days following operation. In three of these, death could be attributed to hemorrhage, while the remaining four presumably died as a result of the myocardial infarction. No control animals surviving operation died during the fourteen day period of observation.

The myocardial infarcts in both the control animals and those receiving Dicumarol were studied in an attempt to distinguish any gross or histologic features that would serve to differentiate these groups. None were found, since the gross and histological findings were similar for both groups. The coronary arteries both above and below the site of ligation were carefully examined to determine the presence of retrograde and centrifugal thrombosis. There was no evidence of propagation of a thrombus in either direction in either group. As far as could be determined, the size of the infarcts was roughly equal in both groups. The endocardium was studied with special care for evidence of mural thrombi or endocardial reaction. Mural thrombi were not present in any of the hearts of any group, and there was no evidence of endocardial involvement.

Hemorrhage into the infarcted areas was not a prominent feature in either group of animals. The myocardium was infarcted in twenty dogs: Eleven of these received Dicumarol and nine did not. Five of the eleven dicumarolized dogs showed slight to moderate hemorrhage into the infarct and six showed no hemorrhage. Four of the nondicumarolized dogs showed slight to moderate hemorrhage in the infarcted myocardium and five did not.

The electrocardiographic changes comprised, singly or in combination, RS-T segment displacements, changes in the direction of the T waves, ectopic rhythms, and conduction disturbances. They were quite typical of those noted

in similar ligation experiments described in the literature.⁹⁻¹⁸ The RS-T segment deviations generally consisted of elevation of the RS-T segment in Leads I and IV and depression of the RS-T segment in Leads II and III. Several variants of this pattern were encountered and are indicated in Tables I and II. Because of the mobility of the dog's heart and the difficulty of placing the precordial electrode in exactly the same position at each reading, much more significance was attributed to changes in the conventional limb leads than in the precordial lead. The displacements generally returned to the isoelectric line before the end of the two weeks' period of observation, but there was an unexpectedly high incidence of persistent RS-T displacement at the end of this period. This finding remains unexplained.

In about one-half of the dogs, T_2 and T_3 , which were originally inverted, became upright; in the other half, originally upright T_2 and T_3 became inverted. Such changes might occur with or without displacement of the RS-T segment. In view of the possibility of spontaneous reversal of the T waves in one or more leads,¹⁹ this type of change has been largely omitted from the protocols. Since records were not made during actual ligation of the coronary artery, the brief "ischaemic" T-wave reversals described by Bayley and La Due²⁰ were not noted.

The ectopic rhythms consisted of ventricular premature beats, singly or in salvos, ventricular tachycardia, and auricular premature beats. The conduction disturbances, sinoauricular block or the various degrees of auriculoventricular block, were relatively infrequently encountered.

It is quite clear from the data presented that no fewer instances of, and no lesser degree of, RS-T segment displacement, conduction disturbances, or ectopic rhythms developed in the treated than in the untreated group. No electrocardiographic or pathologic evidence is at hand that Dicumarol has a favorable effect on the evolution or outcome of established experimental myocardial infarction.

Certain limitations of the experiments should be pointed out. (1) In these animals, the coronary blood vessels other than the ligated artery were healthy, patent, and elastic; whereas in clinical coronary occlusion the collateral vessels may be atherosclerotic, calcified, and narrowed or occluded. (2) The experimental occlusions in these animals were sudden and total, while in clinical coronary occlusion there is a body of evidence pointing to the possibility that in some cases closure is not abrupt and complete, but takes place over a period of time during which the anticoagulant might percolate through the partially occluded area. (3) In three dogs in Group IV (ligation and Dicumarol), hemorrhage was either the sole or a contributory cause of death. The surgical procedure which they had undergone and the use of the anticoagulant made these animals especially vulnerable to hemorrhage, and thus unduly and unfavorably affected the mortality rate. These deaths resulting from hemorrhage have no clinical counterpart since surgery during an attack of coronary occlusion is rare. (4) In spite of the large amount of work represented in these experiments, only twenty-two ligation experiments were finally considered satisfactory for the purpose of the study. Such a limited group is not suitable for statistical analysis.

SUMMARY

The descending branch of the left coronary artery was ligated in two groups of dogs. One group received Dicumarol following ligation, while the second, or control group, received no Dicumarol. The electrocardiographic and pathologic changes were studied in both groups. No significant differences were found.

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CLINICAL ANALYSIS OF THE S WAVE PATTERN ELECTROCARDIOGRAM

AN INVESTIGATION INCLUDING EXTENSIVE UNIPOLAR LEAD STUDIES

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SEVERAL articles have been published which were concerned with the electrocardiogram showing prominent negative deflections in all standard leads. These tracings can be divided into two groups; one in which an initial negative deflection (Q wave) contributes the negative component in one or more leads, and a second group in which the negative deflection is contributed by the S wave in all leads. It is with the latter group that this paper is concerned.

Electrocardiograms of the first type have been found to be commonly associated with serious heart disease; with infarction by Willius,¹ and Bainton and Burstein,² and with bundle branch block by Wilson and associates.³ Burstein and Ellenbogen,⁴ as well as Goldberger and Schwartz,⁵ included both types of tracings in their studies and confirmed the gravity of the first pattern. Schwartz and Marcus⁶ concluded that the negative deflection pattern was due to enlargement of the right ventricle, causing longitudinal rotation of the heart.

Ashman and Hidden⁷ and Wilburne and Langendorf⁸ confined their studies to the S-wave pattern and segregated those tracings showing only this abnormality from grossly abnormal tracings. They concluded that this pattern was most frequently a normal variant, and the former authors believed it characteristic of a relatively vertical cardiac position.

This study was undertaken in an attempt to clarify the following points: (1) Is it true that heart disease is relatively infrequently associated with the S-type electrocardiogram? (2) If so, in those cases with S-wave electrocardiograms, can the unipolar limb leads and/or the precordial chest leads be of aid in further segregating those cases with heart disease from those with normal hearts?

PROCEDURE

Criteria used in selection of electrocardiograms were as follows:

1. Prominent S waves in the three standard limb leads. The S waves had to be 25 per cent or more of the R waves.

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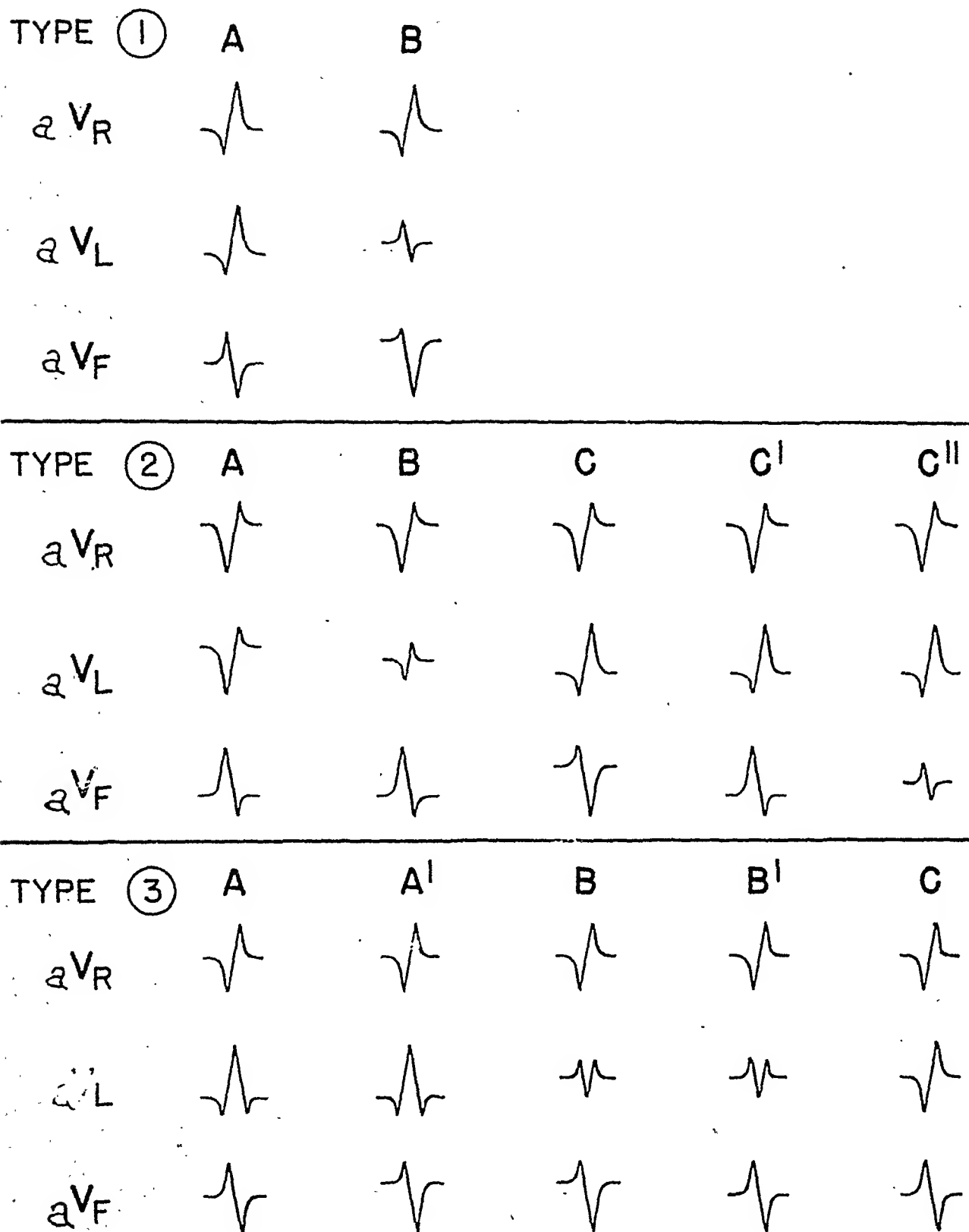


Fig. 1.—Diagrammatic illustration of unipolar limb lead patterns as described in text.

2. Tracings with low, splintered QRS complexes in Lead III were excluded. Tracings with low (>4 mm.) equiphasic QRS complexes in Lead I were included.
3. Tracings with definite abnormalities, such as Q waves, wide QRS complexes (.12 second or more), or abnormalities of the terminal segments were excluded.
4. Tracings with abnormal CF_4 leads were excluded.

Fifty-two consecutive cases presenting the S-wave pattern were studied intensively during 1945 and 1946. Using the technique of Goldberger¹³ unipolar limb leads, precordial leads, and right upper quadrant and left upper scapular leads were taken on all cases. Wherever available, chest x-rays were reviewed and the anatomic axis measured as follows: The relation of the anatomic axis of the heart to an element in the median sagittal plane of the body was determined from teleroentgenograms of the chest by drawing a median line through the center of the bodies of the thoracic vertebrae, then another line from the depression formed by the root of the aorta and the right auricle to the point of greatest curvature at the apex, and measuring the angle formed by these two lines. This angle was then subtracted from 90° to express the anatomic axis in reference to the horizontal plane.

The unipolar limb lead patterns were classified as follows (see Fig. 1):

Type 1: In Lead aV_R , the upright phase was definitely greater than the inverted phase ($R>Q$). The pattern in the other aV leads varied: *A*, In Lead aV_L , the R wave exceeded the Q wave ($R>Q$); in Lead aV_F , the upright and negative phases were approximately equal. *B*, In Lead aV_L , the voltage was low; in Lead aV_F , the S wave exceeded the R wave ($S>R$).

Type 2: In Lead aV_R , the inverted phase definitely exceeded the upright phase ($Q>R$). In the other aV leads the following combinations existed: *A*, In Lead aV_L , $Q>R$; in Lead aV_F , $R>S$. *B*, In Lead aV_L , low voltage; in Lead aV_F , $R>S$. *C*, In Lead aV_L , $R>Q$; in Lead aV_F , $S>R$. *C'* In Lead aV_L , $R>Q$; in Lead aV_F , $R>S$. *C''*, In Lead aV_L , $R>Q$; in Lead aV_F , low voltage.

Type 3: In Lead aV_R , the negative and positive phases were approximately equal. In the other aV leads, the combinations of the negative and positive phases were: *A*, In Lead aV_L , $R>Q$; in Lead aV_F , equiphasic. *A'*, In Lead aV_L , $R>Q$; in Lead aV_F , $S>R$. *B*, In Lead aV_L , low voltage; in Lead aV_F , $S>R$. *B'*, In Lead aV_L , low voltage; in Lead aV_F , S and R equal. *C*, In Lead aV_L , equiphasic; in Lead aV_F , equiphasic.

RESULTS

In addition to making the preceding analysis, we reviewed all of the tracings taken by us at Hines Hospital during the year 1942. Of the 7,571 tracings studied, eighty-two (1.1 per cent) fulfilled our criteria. This figure is probably somewhat low since these tracings were taken on an older age group, the patients, in the main, being veterans of World War I. A comparison of incidence shows that in Ashman and Hidden's⁷ series the incidence was 1.3 per cent after the

abnormal tracings were discarded. Similarly, the incidence in Wilburne and Langendorf's⁸ series became 2.3 per cent. All in all, one can expect to find the S-type pattern in about 2 per cent of all normal tracings in all age groups.

The fifty-two cases studied were a consecutive series upon which electrocardiograms had been routinely taken during 1945 and 1946, and which met our criteria. The age distribution was as follows: The youngest subject was 19 years and the oldest 83 years of age. The greatest number (twenty-five) were found in the 50 to 59 year group. There were eleven in the 20 to 29 year group, four in the 30 to 39 year group, nine in the 40 to 49 year group, and only one in the 60 to 69 year group.

TABLE I. CORRELATION OF UNIPOLAR LIMB LEAD PATTERNS WITH PRESENCE OR ABSENCE OF CARDIOVASCULAR AND PULMONARY DISEASE

TYPES	TOTAL NO.		HEART DISEASE				SYSTEMIC HYPERTENSION		PUL-MONARY DISEASE ONLY		WITH NO CARDIO-VASCULAR OR PUL-MONARY DISEASE	
			RHEU-MATIC	HYPER-TENSIVE	PUL-MONARY	UN-KNOWN	ONLY	WITH PUL-MONARY DISEASE				
1												
A	5			3				1		1		
B	8				2	1				2	3	
Total		13				6		1		3		3
2												
A	5		1							1	3	
B	7					1		1			5	
C	6			1						2	3	
C'	2										2	
C''	5			1						1	3	
Total		25				4		1		4		16
3												
A	2										2	
A'	2										2	
B	4										2	
B'	4		1				1			2		
C	2				1						1	
Total		14				2		1		4		7
Total		52				12		3		11		26

Table I is a summary of the pertinent findings in this study. Several suggestive correlations can be noted. Of the fifty-two patients studied, twelve (23 per cent) had heart disease, as compared with 37 per cent in the series of Wilburne and Langendorf.⁸ Etiologically, five had hypertensive heart disease, three had cor pulmonale, two had rheumatic heart disease, and in two cases the etiology was unknown. There were three patients with systemic hypertension who did not have heart disease. One patient had hypertension only,

while the other two had associated pulmonary disease. Eleven patients (21.2 per cent) had pulmonary disease only, and twenty-six patients (50 per cent) had neither cardiovascular nor pulmonary disease. The latter group presented the usual varied conditions found in a large general hospital in which the diagnosed diseases had no bearing on the configuration of the electrocardiogram.

The cases showing the Type 1 pattern seem of special significance. Of the five patients under Type 1,A, one had systemic hypertension and pulmonary disease, one had pulmonary disease only, and three had hypertensive heart disease. The pulmonary disease in both instances was asthmatic bronchitis. The pattern in Type 1,A is characterized by tall R waves in aV_R and aV_L , and by an equiphasic leg lead. The chest leads were not unusual or distinctive in any way; this was found to characterize the chest leads of all the cases in this study. The anatomic axis was 40° or less in four of these five patients. The fifth patient was a 55-year-old man with both asthmatic bronchitis and systemic hypertension, in whom the anatomic axis was 47° . The most transverse heart had an axis of 28° . The unipolar leads taken from the left upper scapular area showed R waves which were all 4 mm. or more in height. One patient also showed an R wave in the right upper quadrant lead which was 6 mm. tall. This would tend to support Goldberger's¹² contention that an R wave of 4 mm. or more in the left upper scapular lead is indicative of left ventricular hypertrophy.

Of the eight patients whose tracings conformed to Type 1,B, three had heart disease. The etiology in two patients was cor pulmonale, while in the third, the etiology was unknown. Two patients had pulmonary disease only. The remaining three patients had neither pulmonary nor cardiovascular disease. Thus, four subjects were found to have some type of pulmonary disease. X-ray films of the chest were available in seven of these patients. The anatomic angle was close to 40° in five of these, and 50° in the remaining two. Only one patient showed an R wave of at least 4 mm. in the left upper scapular lead and this was a patient admitted for a head injury who had neither hypertension nor pulmonary disease. One of the patients with cor pulmonale had an R wave of 7 mm. in the right upper quadrant lead, but the other patient had a low, splintered QRS complex in this same lead.

Type 2 proved to comprise the largest number of patients in the series. There were twenty-five cases in this group, all well scattered among the subgroups. Four patients had heart disease: two had hypertensive heart disease; one, rheumatic; and in one, the etiology was unknown. There was one patient with systemic hypertension and asthmatic bronchitis. There were only four patients with pulmonary disease in this group. One of these was a 31-year-old man with an R wave in the right upper quadrant lead of 6 millimeters. The diagnosis was asthmatic bronchitis, and there was no evidence of heart disease. The anatomic axis was 55° . The one patient with rheumatic heart disease had an R wave of 5 mm. in the right upper quadrant lead, and the anatomic axis was 39° . Only one patient with the Type 2 pattern had an R wave of 4 mm. in the left upper scapular lead. This was a 49-year-old man who was admitted for treatment of cholecystitis. No chest x-ray was available. The chest leads

revealed inverted T waves on the left side of the precordium. A clinical diagnosis of heart disease had not been made in this patient. In the entire group, x-ray films of the chest were available for study in sixteen patients. The anatomic axes in this group varied from 55° , as mentioned in the first patient described, to 28° in the patient with the undetermined type of heart disease; in the remaining fourteen patients, the axes were well scattered between these extremes. There was no obvious clinical correlation here.

Type 3 included fourteen cases, well scattered among the subgroups. There were two patients with heart disease, one with rheumatic disease, and one with pulmonary hypertension. The latter belonged to Type 3,C and had the primary diagnosis of bullous emphysema. X-ray films were not available in this patient. The chest leads revealed an M-shaped QRS complex in leads over the right side of the precordium. The right upper quadrant and left upper scapular leads were not abnormal. The only patient with systemic hypertension (unaccompanied by pulmonary disease) was found in this group. The four patients with a Type 3 pattern who had pulmonary disease fell into the subgroups *B* and *B'*. Two of these patients had R waves of 4 mm. in the right upper quadrant leads, whereas the other two had R waves of 4 mm. and 3 mm., respectively, in the left upper scapular leads. The diagnosis in three of these patients was chronic pulmonary tuberculosis, and in the fourth, asthmatic bronchitis. There was one patient in Type 3,B who had an R wave of 5.5 mm. in the right upper quadrant lead. This was a 20-year-old man who was admitted for treatment of hemorrhoids. Eight x-ray films were available in the Type 3 group. The two patients with a Type 3,A' pattern were interesting in that the anatomic axes were 28° and 26° . In the others the axes varied from 49° to 35° , with no apparent clinical correlation.

The standard limb lead electrocardiograms were also studied from the point of view of depth of the S waves. Thirty-six cases were found in which the amplitude of the S waves was at least 50 per cent that of the R waves in all the standard leads. Of these, fifteen patients had a clinical diagnosis of pulmonary disease. Since there were only sixteen cases in all with pulmonary disease, this group for all practical purposes contains all the cases with pulmonary pathology. In ten of the thirty-six cases the S waves were equal to, or greater than, the R waves in each lead. Six of these patients were found to have some type of pulmonary disease. The other four patients had no clinical correlation. The incidence of pulmonary disease in this group was 60 per cent, or about twice that of the incidence of pulmonary disease in the entire series (sixteen out of fifty-two, or 30.8 per cent). It appears from this survey that the greater the depth of the S waves the greater the correlation with pulmonary disease.

In the sixteen patients with pulmonary disease, x-ray films of the lungs were available in twelve. Only four patients had anatomic axes between 55° and 45° . In the remaining eight patients the axes ranged from 44° to 35° , five cases being less than 40° in five patients. In the twenty-six cases with neither pulmonary nor cardiovascular disease, x-ray films were available in sixteen

cases. Only three patients had anatomic axes greater than 45° , and only six had axes greater than 40° . From these data, it appears that a relatively vertical axis was not a frequent occurrence in the group with neither cardiovascular nor pulmonary disease, nor in the group with pulmonary disease alone.

DISCUSSION

In considering any electrocardiographic pattern it is always desirable, if possible, to make certain clinical correlations in order that practical applications may be made. Very early it was evident from inspection of the standard leads in which an S-wave pattern was present that no such correlations were possible.

LaDue and Ashman⁹ have recently indicated the types of QRS deflections which should be found with the variations of the position of the heart in relation to its three axes. From the S-wave patterns shown, it is inferred that with a transverse heart and marked counterclockwise rotation, S waves increasing in depth from Lead I to Lead III may be found; while in the heart with normal position on its long axis and the apex posterior, S waves decreasing in depth from Lead I through Lead III may be found. An attempt to make such a correlation in the present series was a failure. It is evident from our study that several causes may give rise to the S-wave pattern in the standard leads. Circumstances under which the right ventricle is overburdened as well as those in which there is left ventricular hypertrophy may do so. An S-wave pattern was also prominent in a group of patients with pulmonary disease, but without definite heart disease. There is a small group of patients with systemic hypertension without evident heart disease who show an S-wave pattern. There is also a large group, one-half displaying the S-wave pattern, in whom no evidence of cardiovascular nor pulmonary disease is present. In our experience, the standard limb leads or precordial leads do not furnish any information which makes any distinction of clinical nature possible.

A study of these cases by unipolar leads was undertaken in the hope that some additional information of practical clinical importance might be obtained. On the whole this was also disappointing. Multiple unipolar precordial leads gave no information. The unipolar limb leads gave us only one significant pattern (Type 1). Only three of the thirteen patients in this group were free of cardiovascular or pulmonary disease. One-half of the patients having heart disease in the entire series fell into this small group. Therefore, when Lead aV_R shows a positive deflection greater than the negative deflection, it is strong presumptive evidence that cardiac disease, pulmonary disease, or both, are present. If, in addition, Lead aV_L shows a high R wave and Lead aV_F is equiphasic, it is strong evidence that left ventricular hypertrophy is present. In no case of right ventricular hypertrophy did this latter pattern occur. With respect to the unipolar limb lead patterns under Types 2 and 3, it can only be concluded that heart disease was comparatively rare, being present in only six of the thirty-nine patients. Hypertension without heart disease was present in two of the thirty-nine, while pulmonary disease was found in eight. Slightly over one-half (twenty-three) had no evidence of cardiovascular or pulmonary disease. How-

ever, no correlation could be found which would aid in distinguishing those with disease from those with no disease.

It is also apparent that in all cases of hypertensive heart disease, the voltage of the R wave strikingly exceeded the voltage of the Q wave in Lead aV_L , irrespective of the pattern exhibited by Lead aV_R ; while in right ventricular hypertrophy, Lead aV_L was either equiphasic or the Q exceeded the R wave in voltage, irrespective of the patterns exhibited by Leads aV_R and aV_F . This is of little aid in clinical application, since both criteria were frequently met by patients who had no disease.

From the findings in this series of cases, it is our impression that normal position or a tendency toward vertical position of the heart with the apex rotated posteriorly is the most common cause of the S-wave pattern. In chronic pulmonary disease with associated emphysema, the depression of the diaphragm with extension of the lungs into the anterior cardiac space can well be responsible for such a cardiac position. In the congenital vertical heart, the long axis tends to rotate posteriorly as the vertical position is assumed and produces relatively the same cardiac position. Also, it is probable that in some patients with heart disease involving either the right or left ventricle, this cardiac position is the major factor in determining the distribution of the potentials to the extremities in such a manner as to give rise to the S-wave pattern in the standard leads. That such a position of the heart is not always responsible for the S-wave electrocardiogram is evident from the markedly transverse position of the heart found in patients with hypertensive heart disease. Under these circumstances, marked counterclockwise rotation with the apex displaced posteriorly is probably the explanation.

Various authors have commented on the possible etiology of the S-type electrocardiogram. Gardberg and Ashman,¹⁶ in their study of possible QRS patterns by vector analysis, state that the S-type electrocardiogram is "by no means uncommon" in persons with so-called "dropped heart." They point out that an important factor is that the apex is pushed posterior, or the base pulled forward, with the result that the mean QRS axis points backward and upward. They add that "some distortion of the electrical fields by the thoracic configuration and by the lungs may not contribute a little to the relatively backward direction of the mean QRS axis. We do believe that such factors are of secondary importance."

Wilson and associates¹⁵ recognized the possible role of right ventricular hypertrophy in the etiology of the S-type pattern. They state, "When the heart is in the semivertical position, . . . right ventricular hypertrophy produces large S waves in all the standard limb leads." Goldberger and Schwartz⁵ state that in five of their cases "there was evidence of enlargement of the right ventricle, or of conditions in which right ventricular hypertrophy might be expected (asthma and pulmonary tuberculosis)." Schwartz and Marcus⁶ collected eight autopsied cases with similar patterns; seven had pulmonary tuberculosis and "merely showed right ventricular hypertrophy or dilatation at autopsy." That right ventricular hypertrophy may be occult has been a common experience of

clinicians, and details can be found in the studies by Master¹⁷ and Sussman and associates.¹⁸ In our series of fifty-two cases, the diagnosis of cor pulmonale was made in only three instances, but it is impossible to state how frequently right ventricular hypertrophy was actually present in the thirteen patients with pulmonary disease. Only a more comprehensive study could accurately determine the importance of right ventricular hypertrophy as an etiological factor in the S-wave pattern.

The theoretical possibility of extreme left axis deviation producing an S-type electrocardiogram was recognized by Goldberger and Schwartz. They postulate that "the electrical axis would have to rotate counterclockwise to at least -120° ." They show one case in which this tendency was present.

That the right ventricle is notably elusive to both clinical and x-ray examination has been commented upon. This elusiveness prevails in the field of electrocardiography. This is due to the fact that there must be a great increase in the muscle mass of the right ventricle before potentials derived from its activation are able to overcome the normal preponderance of potentials derived from the left ventricle and so alter the electrocardiogram. By use of the right upper quadrant and left upper scapular unipolar leads, as advocated by Goldberger, we attempted to determine if this difficulty might be decreased. Our findings indicate that a low R wave in the left upper scapular lead or a low-voltage biphasic complex indicates that left ventricular hypertrophy is not present. This also suggests that the relative magnitude of potential derived from the right ventricle may be greater than normal. It should be kept in mind, however, that a heart in unusual clockwise rotation around its long axis may project potentials from both the right and left ventricles toward the left shoulder, and give an intermediate type of complex. A prominent R wave in the right upper quadrant lead is strongly suggestive of right ventricular hypertrophy. However, in other observations we have made on patients with definite mitral stenosis and chronic cor pulmonale, only a minority showed such a right upper quadrant pattern. Likewise, patients in whom there is no clinical reason for right ventricular hypertrophy may rarely show a prominent R wave in the right upper quadrant lead. It is our belief that occasionally the cardiac position may be such that the potential picked up by a right upper quadrant lead may be for the most part derived from the left ventricle producing a prominent R wave. Our experience indicates that the right upper quadrant and left upper scapular leads are of very limited value in determining the presence of hypertrophy of either ventricle.

It was noted that the S-wave pattern may be transient, tending to wax and wane in an occasional patient. We could not correlate this change with any gross anatomic deviation such as pleural or pericardial fluid, as was pointed out by Burstein and Ellenbogen.⁴

SUMMARY

A study of otherwise normal electrocardiograms of fifty-two patients showing S waves in all standard limb leads was carried out, using precordial leads,

six unipolar limb leads, and right upper quadrant and left upper scapular unipolar leads. The S waves in the standard limb leads were 25 per cent or more than the R deflection in the same lead.

The clinical diagnoses in fifty-two patients were heart disease in twelve, hypertension alone in one, pulmonary disease alone in eleven, and hypertension and pulmonary disease together in two cases, while in twenty-six patients there was no disease present which would influence the electrocardiogram.

The only positive correlation which was noted from inspection of the standard limb leads was that when the S-wave deflections were of considerable magnitude in all leads there was a high incidence of pulmonary disease.

Unipolar lead studies were made in an attempt to establish criteria for differentiating patients with disease from those without disease and for correlating the electrocardiographic findings with the clinical findings. The multiple unipolar precordial leads offered no assistance in this respect. By grouping the various patterns noted in the unipolar limb leads, it was found that the pattern designated as Type 1 was associated with a very high incidence of cardiovascular or pulmonary disease. The remaining types did not contribute any further information. The unipolar leads from the right upper quadrant and left upper scapular areas were of no more than slight value in determining the presence of hypertrophy of either ventricle.

It is probable that the fundamental factor in determining the presence of S waves in the standard limb leads is the position of the heart. A tendency toward a vertical position with the apex displaced posteriorly is the most common cause. A heart in a transverse position with marked counterclockwise rotation on its long axis rarely will give rise to such a pattern. Cardiac or pulmonary disease is active in producing the pattern only insofar as it may contribute to such cardiac positions. In one-half of the patients studied, this electrocardiographic pattern was a normal characteristic of the individual. It is concluded from this study that such extensive unipolar lead investigations are impractical as a routine clinical procedure because of the relatively little clinical value that they yield.

Tracings meeting the criteria used in this paper are obtained in approximately 2 per cent of all electrocardiograms taken on adults.

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Clinical Reports

"ANGIOMESOHYPERPLASIA": A GENERALIZED NONINFLAMMATORY OCCLUSIVE ARTERIAL DISEASE

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WHILE occlusive vascular disease syndromes have frequently been described in white men, this form of disease has been relatively rare in the Negro. Some investigators are convinced that thromboangiitis obliterans has been found in Negro men,¹ but most writers in the field are unwilling to recognize such an entity in them. Recently, a new form of occlusive vascular disease has been reported by Yater and Roberts.² In the two patients recorded by these authors, the clinicopathologic picture of unknown cause differs from the usual Buerger's or arteriosclerotic vascular disease. The case which we are presenting demonstrates still another variation of arterial disease which may be, but is probably not, a variation of the entity described by Yater and Roberts.

CASE REPORT

T. L., a 43-year-old Negro janitor entered the Hutchinson Memorial Clinic of Tulane Medical School on Sept. 27, 1945, complaining of pain in the left calf on walking more than two blocks, and an intermittent "heavy feeling" over the precordium associated with burning pains radiating along the medial aspect of the left arm. The present illness began about three years prior to admission. Initially, he had a "tired" feeling in the calves of his legs. The discomfort progressed gradually to the cramping of intermittent claudication. The latter developed about seven months before coming to the Hutchinson Clinic. One year prior to admission, he noticed heavy sensations over the precordium on moderate exertion. The first severe attack occurred two months before admission. At that time, he had a severe crushing precordial pain which occurred after his evening meal and lasted twelve hours. The pain was accompanied by nausea, sweating, and dyspnea. He remained in bed the following day, but he was able to resume regular work thereafter. Subsequent to this episode of pain he continued to have precordial discomfort, with pain radiating along the medial aspect of the left arm on slight exertion or excitement. These attacks usually lasted ten to fifteen minutes. In the past he fainted on two occasions without any known prodromata or sequelae; in both instances, the syncope followed paroxysms of coughing. His vision had been impaired for several years. There were no headaches, vertigo, ataxia, epistaxis,

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hemoptysis, pulmonary disease, or complaints referable to the gastrointestinal or genitourinary systems. His family history was irrelevant. For years he had been smoking as many as twenty cigarettes daily, but rarely consumed alcohol.

Physical examination revealed a moderately obese, middle-aged Negro man, who appeared anxious about his condition. The pulse rate was 92, respiratory rate, 20 per minute, and the blood pressure was 158/100. The physical examination was essentially normal. The salient findings follow. The retinal arteries were slightly sclerotic. The apex impulse was not visible; the point of maximum impulse was palpable in the fifth intercostal space in the midclavicular line. The cardiac rate and rhythm were normal. A faint systolic apical murmur heard initially was not present on subsequent examinations. The reflexes were equal bilaterally, but hypoactive. The extremities showed both legs to be rather cold, but the left was colder. No varicosities, abnormal pigmentation, nor trophic changes were noted. The pulsations of the dorsalis pedis, posterior tibial, and popliteal arteries were absent bilaterally; the femoral arteries pulsated feebly. The common carotid arteries pulsated normally, while the radial and temporal arteries showed decreased pulsations.

Laboratory Data.—The urine on repeated examinations was normal. Urine concentrations reached values from 1.024 to 1.027. The nonprotein nitrogen of the plasma was 40 mg. per 100 cubic centimeters. The hemogram on admission revealed 5,400,000 erythrocytes; 90 per cent hemoglobin, and 10,200 leucocytes with a normal differential count. Blood serology was negative. A teleroentgenogram was normal. Both legs and feet failed to show calcification of the vessels or bone changes on x-ray examination. The initial electrocardiogram (Sept. 27, 1945) showed typical changes of an old posterior infarct. Four subsequent tracings revealed considerable improvement (Fig. 1).

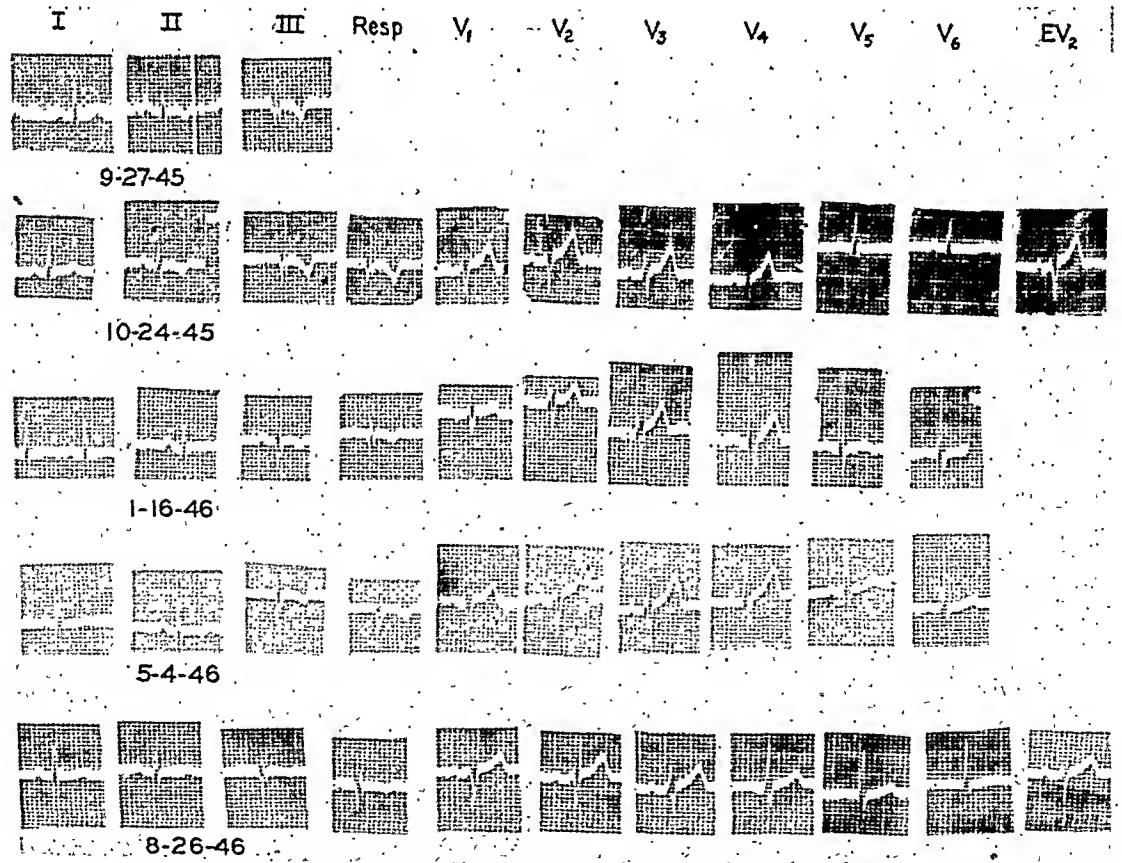


Fig. 1.—The serial electrocardiograms show an old posterior infarct with a gradual return toward normal.

ADDITIONAL OBSERVATIONS

Histologic Study.—On November 14, a biopsy was made of the left posterior tibial artery. At the time of surgical removal of a segment of this artery, it was found to be cordlike, free from evidences of periarterial inflammation, and, on severance, no blood flowed from the cut ends. Due to misunderstanding, a segment of vein was not removed and because of the impaired circulation to the part and marked delay in healing (eight months) at the site of arterial biopsy it was deemed inadvisable to subject the patient to another biopsy to obtain a segment of vein.

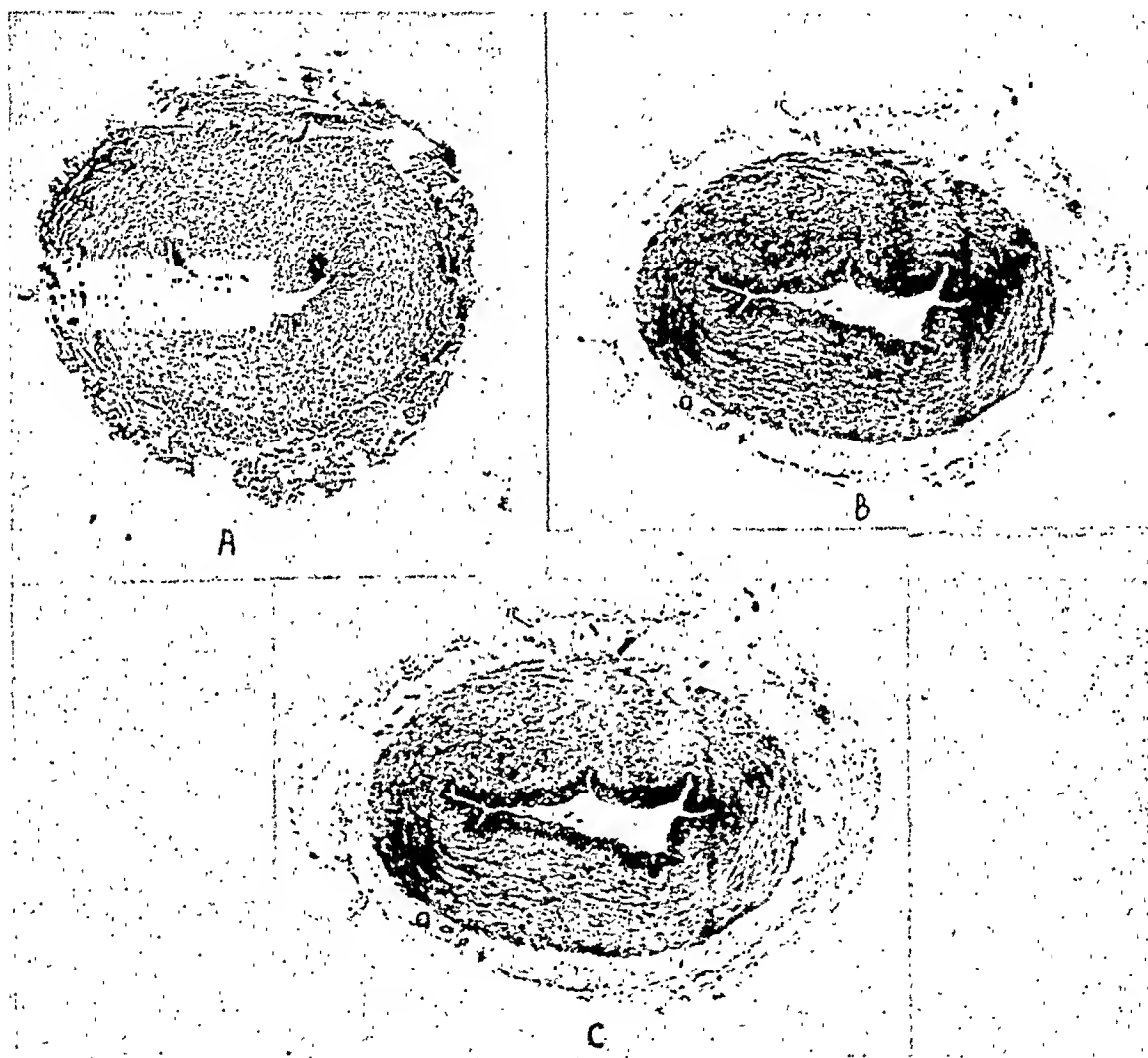


Fig. 2.—Sections of a segment of the left posterior tibial artery removed at biopsy. A is stained by the hematoxylin-eosin method, B and C by Verhoeff's elastic stain. Consult text for details.

The segment of artery was sent to Dr. Charles Dunlap,* who is responsible for the histologic examinations (Fig. 2) and the following report.

"The specimen consists of a segment of artery 2.4 cm. long and 0.2 cm. in diameter. One end is flattened and shows the marks of forceps. The adventitia is smooth, white, and glistening. The arterial wall is thickened, tough, and

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rubbery. Multiple transverse cuts reveal a small lumen varying from a slitlike opening measuring 0.1 cm. in greatest diameter to a minute round opening of pinhole caliber. There is no corresponding variation in the external diameter of the vessel.

"Segments of the artery taken at five different levels were sectioned and stained with hematoxylin and eosin, Verhoeff's elastic tissue stain, and Mallory's aniline blue. Microscopic examination reveals remarkably little in the way of pathologic change apart from a thickened media and a small lumen. No inflammation is present. The endothelium appears normal. The intima is rich in elastic fibrils, but is not thickened. The media is thickened in relation to the diameter of the vessel and the caliber of the lumen. The media is normal histologically, being composed principally of smooth muscle fibers with scattered elastic tissue fibrils. The connective tissue stain shows no more than the normal amount of collagen. The adventitia of the vessel is made up of coarse bundles of collagen instead of the usual delicate fibrous reticulum. Small blood vessels are numerous in the adventitia, and elastic tissue fibrils are somewhat more abundant than usual.

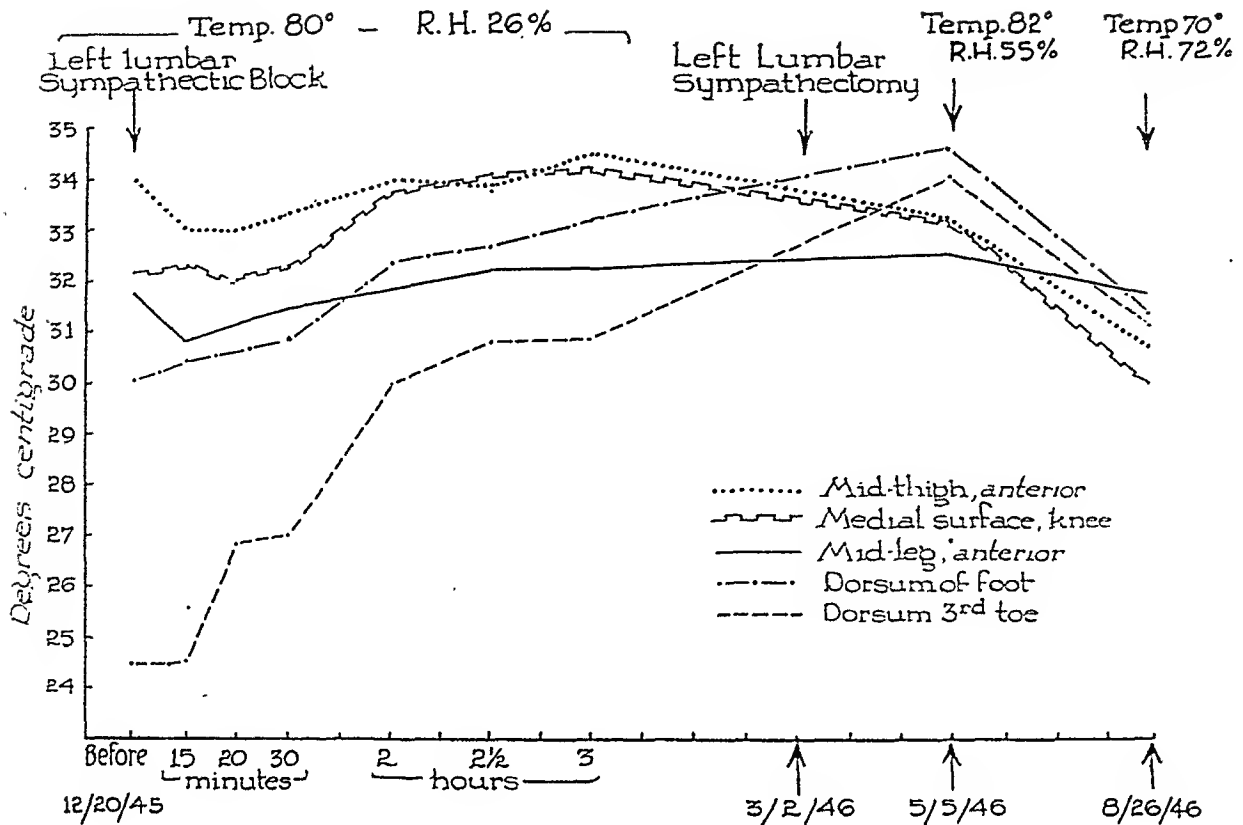
"No specific diagnosis can be made. The principal findings are a relative thickening of the media and a noninflammatory fibrosis of the adventitia. Although the adjacent vein and perivascular tissues were not available for examination, the changes present in the artery are not of such a nature as to warrant a diagnosis of Buerger's disease. Occlusion of the vessel at a higher level might conceivably have caused these minor changes even though no obliterative endarteritis is present."

Thermocouple Studies: On Dec. 20, 1945, the patient rested recumbent in a hospital type of bed in a draft-free, air conditioned room (temperature 80° F., relative humidity 26 per cent). After a period of sixty minutes' rest, recordings of the skin temperature measurements were made bilaterally for the (1) anterior surface of the mid thigh, (2) medial aspect of the knee, (3) anterior surface of mid leg, (4) dorsum of foot, and (5) dorsum of third toe. After base line levels were obtained, a left lumbar sympathetic procaine block was performed and the changes in skin temperature followed (Fig. 3). It can be seen that the parts which were initially cold gradually warmed. This was true for the left side with the lumbar sympathetic block as well as the right side without block. The dorsum of the left foot was warmer initially than the same area on the right and it, therefore, changed little in temperature with rest in the comfortable room. One is forced to conclude that no change in temperature was produced by the lumbar sympathetic block.

On May 5, 1946, essentially two months after left lumbar sympathectomy, the temperature of both lower extremities was essentially the same, except that the third toe on the sympathectomized side was definitely warmer. The experimental conditions were the same as on Dec. 20, 1945.

On Aug. 26, 1946, the temperature measurements were repeated under identical circumstances, except that the room was made cool (temperature 70° F., relative humidity 72 per cent) in order to ascertain any difference in the

LEFT LEG



RIGHT LEG

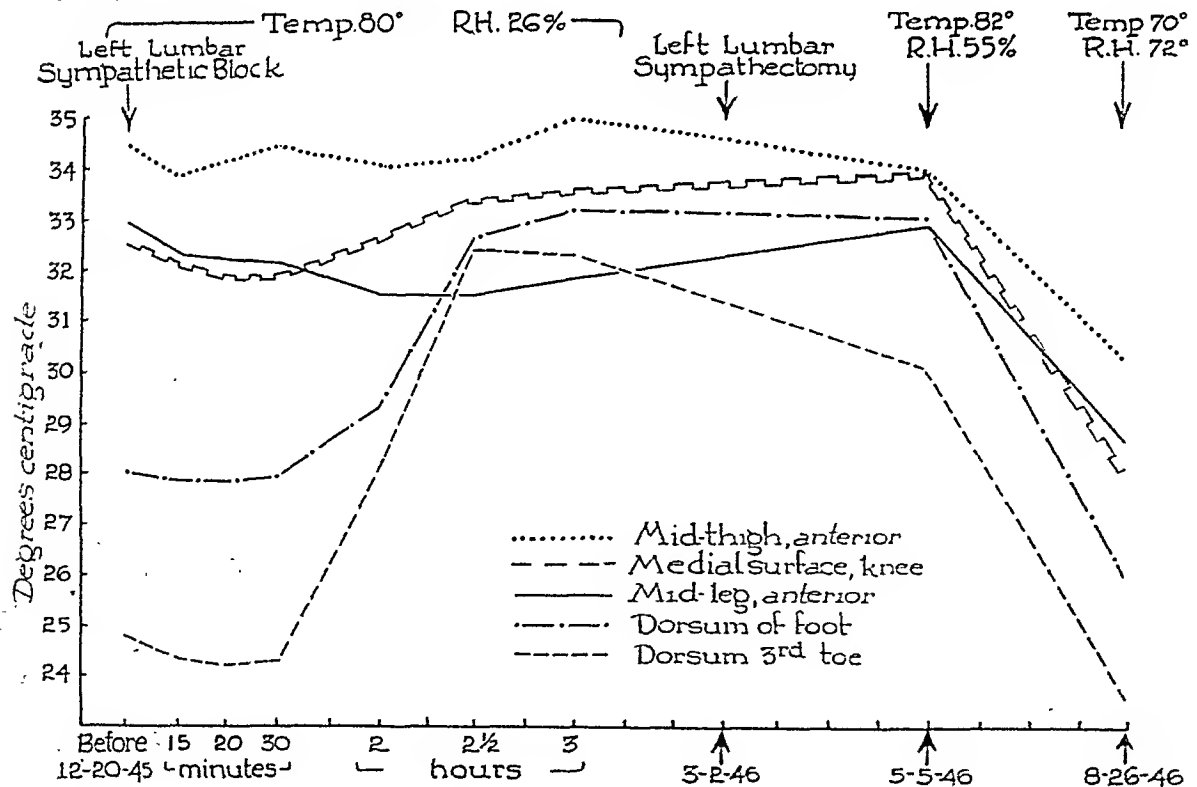


Fig. 3.—Variations in skin temperature recorded for the lower extremities before and after procaine blocking of the left lumbar sympathetic nerves and after left lumbar sympathectomy. There were no significant differences between the reactions in the two extremities. The rise in temperature bilaterally after sympathetic nerve blocking apparently resulted from a gradual warming of previously cold feet. The terminal portions of the records show a more rapid cooling of the right leg in the cool environment than the left sympathectomized one.

rate of cooling of the lower extremities as the patient rested quietly in bed. It is seen in Fig. 3 that the left lower extremity with the lumbar sympathectomy cooled more slowly than the right extremity with an intact sympathetic nervous system, thus indicating a more adequate circulation on the left or sympathectomized side.

The Plethysmograms: Plethysmographic recordings were made simultaneously with the temperature measurements by a method previously described.³ The tips of right index finger and the right and left second toes were observed. The plethysmograms (Fig. 4) showed an absence of *pulse* deflections in the tips of the toes (plethysmograph sensitive to 0.1 c. mm.), while those in the tip of the right finger were normal. The *alpha* deflections were small in the toes and normal in the finger. Sympathetic nerve block by procaine and heat to the entire body failed to change the status of the *pulse* and *alpha* deflections in the toes. Heat increased the *pulse* deflections in the finger (Fig. 4). After left lumbar sympathectomy was performed on March 2, 1946, *pulse* deflections appeared for the first time, although they are barely visible, 0.1 mm. (Fig. 4). Since *pulse* deflections developed bilaterally, although sympathectomy was limited to the left lower extremity, the influence of the operation is difficult to evaluate.

Progress Notes: The patient had been studied over a period of eighteen months. When first seen, a bilateral lumbar sympathetic novocain (1 per cent) block was done. Following this procedure, the patient experienced a sensation of warmth beginning four to five hours after the injection, and he volunteered that he could walk approximately twice the usual distance before developing calf pain. These novocain blocks were repeated on several occasions with the same subjective results. At no time, however, was there definite objective evidence of marked temperature changes nor any demonstration of pulsations which were previously absent. On November 14, a biopsy of the left posterior tibial artery was obtained. The severed end of the artery did not bleed. The patient began to experience pain at rest in the left calf muscles. He received bromides for sedation, aminophylline, and alcohol without any objective or subjective changes in the legs or biopsy wound. Buerger's exercises, novocain blocks, tubbings at body temperature, and leg exercises under water provided but little subjective relief and no improvement in wound healing.

The patient was admitted to Charity Hospital on Feb. 20, 1946. There the clinical findings were essentially the same as before. On March 2, Dr. Mims Gage* performed a left lumbar sympathectomy, resecting the second, third, and fourth lumbar ganglia. Following the sympathectomy, the pain at rest disappeared. The left leg felt warmer than the right leg, but at no time during his hospital stay were there any demonstrable pulsations in the large arteries of the legs. He had an uneventful recovery and was discharged.

He was seen at his home on April 25, 1946. Pulsations were noted for the first time in both dorsalis pedis arteries and in the right posterior tibial artery.

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The left foot and leg were warmer than the right foot to touch. On May 5, 1946, he was examined in the laboratory and further physiologic observations were made. The blood pressure was 120/80. The fundoscopic examination revealed only slight thickening of the retinal arteries. The dorsalis pedis arteries pul-

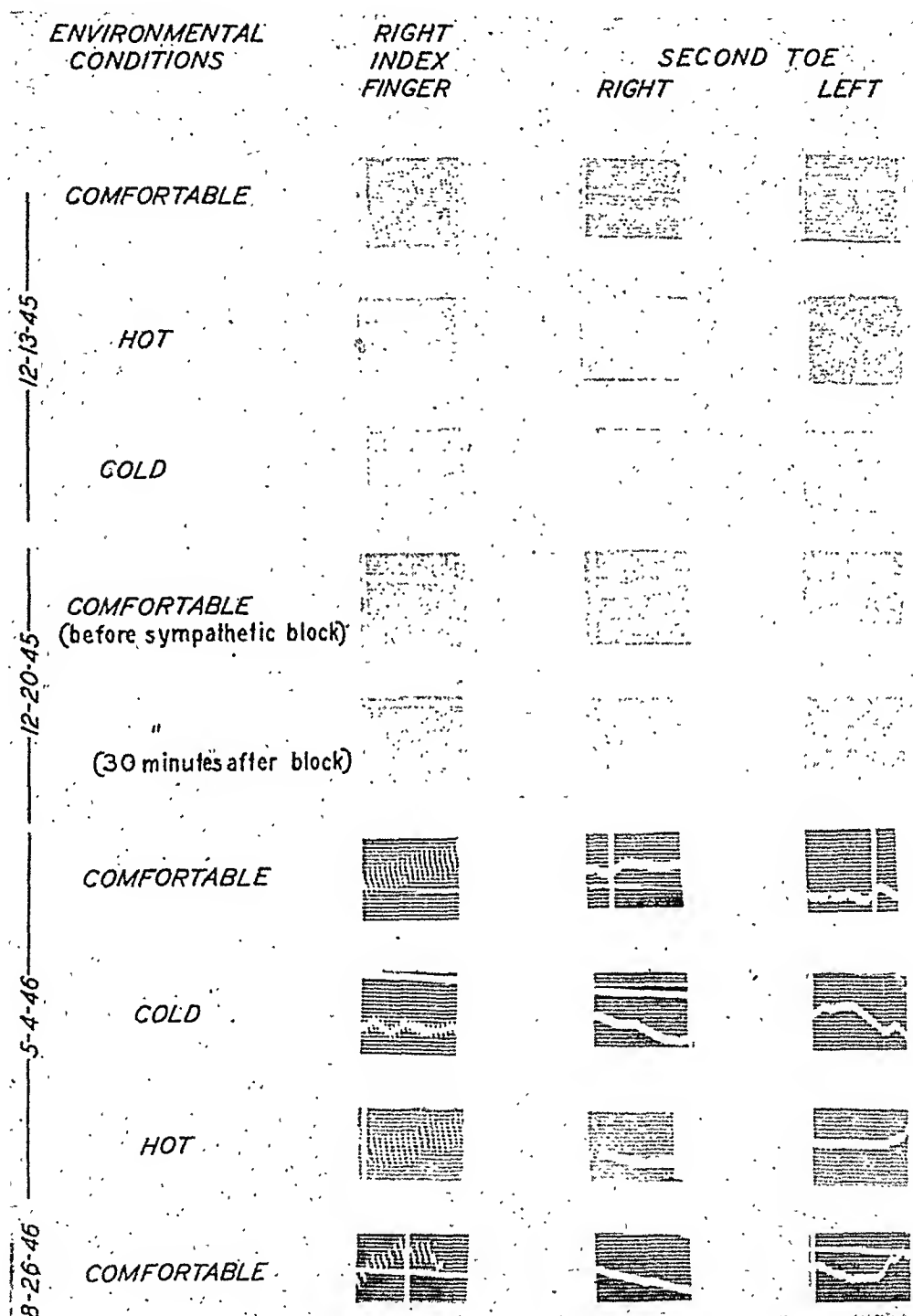


Fig. 4.—Plcthysemograms of the tips of the right index finger and right and left second toes. The pulse and alpha deflections of the finger tips responded to variations in environmental temperature in a normal fashion, while there were no pulse deflections in the tips of the second toes regardless of the temperature changes (Dec. 13, 1945, May 4, 1946). There were alpha deflections in the tips of the toes, however, but they also failed to be changed by temperature variations. Left lumbar sympathetic block on Dec. 20, 1945, likewise produced no pulsatile changes. After left lumbar sympathectomy performed on March 2, 1946, small but definite pulse deflections appeared in the toes and have persisted. This may have been coincidental since they were present bilaterally while the operation was unilateral.

sated, but they were not as strong as they had been ten days previously. The biopsy site had improved but was not healed (approximately six months after the biopsy). The left leg showed atrophy of the muscles but the skin was normal.

He was examined again on Aug. 26, 1946. The ulcer had healed about one month previously, and the surrounding skin was normal. The eyegrounds had not changed since previous observations. The dorsalis pedis artery pulsations were feeble bilaterally. The slight atrophy of the left leg was attributed to disuse.

Except for three slight elevations recorded initially, the blood pressure remained within normal limits during the entire period of observation.

DISCUSSION

The patient described had an organic arterial occlusive disease indicated by the clinical and physiologic observations and biopsy. The biopsy findings showed the disease to be different from thromboangiitis obliterans and more like the condition described by Yater and Roberts.² However, the histologic findings are somewhat different from those described by the latter two observers. In fact, the disease described in this report may be an entirely new one. Unfortunately, circumstances prevented more complete biopsy studies. The fact that this patient was a Negro and the two patients of Roberts and Yater were also Negroes does not constitute sufficient evidence to warrant a conclusion that the white race is free of the disease. It is exceedingly important that more patients be studied in order to establish properly this new disease entity.

The biopsy resulted in a chronic ulcer which healed very slowly. The more rapid rate of healing following the lumbar sympathectomy supports the value of sympathectomy as a therapeutic procedure. This is further supported by the tendency of the sympathectomized leg to remain warm in a cool environment while the other approached room temperature. The presence of essentially equal *pulse* deflections in bilateral plethysmograms does suggest that the disease might have been in a spontaneous remission. The failure of vasodilation to follow sympathetic procaine block is also in support of the latter concept.

That the disease is generalized is evidenced by the occurrence of a coronary occlusion, feeble pulsation in the femoral arteries, and absence of pulsations in the popliteal artery and its branches. There were diminished pulsations in the temporal and radial arteries.

Throughout the period of observation there had been no evidence of change in the renal circulation. The microscopic findings in the urine have been normal and urine has reached concentrations of 1.027. The blood urea nitrogen has remained normal on repeated examinations.

Unlike the patients reported by Yater and Roberts,² our patient had no cerebral vascular episodes nor any symptoms referable to the nervous system except two instances of syncope which followed paroxysms of coughing.

There had been no tenderness over the arteries and veins and the microscopic examination of the artery did not suggest that the disease was inflammatory in nature. Because this disease entity might be more than a medical curiosity and, therefore, confront clinicians in the future, it is considered neces-

sary to tag the syndrome by an appropriate term. Since the syndrome is little known, especially etiologically and only to a very limited extent histologically and physiologically, the noncommittal term "angiomeshyperplasia" is suggested.

SUMMARY

An adult Negro with occlusive vascular disease has been described. The disease was generalized, but affected principally the arteries of the lower extremities and heart. Thermocouple and plethysmographic studies confirmed the occlusive nature of the disease, which was further substantiated by biopsy studies. The etiological nature of the disease is not apparent; therefore, a descriptive name, "angiomeshyperplasia," has been submitted for the syndrome.

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RUPTURE OF THE HEART FOLLOWING ACUTE MYOCARDIAL INFARCTION

INCIDENCE IN A PUBLIC HOSPITAL, WITH FIVE ILLUSTRATIVE CASES INCLUDING ONE OF PERFORATION OF THE INTERVENTRICULAR SEPTUM DIAGNOSED ANTE MORTEM

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RUPTURE of the heart following coronary artery occlusion with infarction has been a pathologic rarity until recent years, and its clinical evaluation has not been well recognized by physicians.

In 1925, Krumbhaar and Crowell¹ made a thorough review of 654 cases of cardiac rupture, including an analysis of twenty-two cases of their own. They concluded that the perforation usually develops in the wall of the left ventricle, that it usually occurs in the aged, and that it is practically always due to coronary disease. They found the lesion to be more frequent in the anterior surface of the left ventricle following acute coronary artery thrombosis, and less frequent in slow occlusion of these vessels. Rupture of a ventricular aneurysm from a chronic infarct is a rarity. In 1940, Martland² reported forty-two cases of rupture of the heart among 2,000 patients who had died suddenly. In the 2,000 cases, coronary occlusion with thrombosis was encountered in 304, and "coronary insufficiency" in 112. There were 59 aneurysms of the left ventricle, but none ruptured. Thus, 13.8 per cent of all cases presenting acute coronary artery thrombosis with fresh infarction, and 5.75 per cent of all patients suffering from coronary heart disease, died from cardiac rupture. In 1942, Edmondson and Hoxie³ found an incidence of 8 per cent of cardiac rupture among 865 cases of recent myocardial infarction in an analysis of 25,000 patients upon whom necropsies had been performed. In 1944, Friedman and White⁴ reported 270 cases of myocardial infarction, 105 recent and 165 healed. Among the healed lesions, numerous ventricular aneurysms were observed without a single rupture. Of the 105 cases of recent infarction, rupture of the heart occurred in ten instances (9.5 per cent). In every case, the mechanism of death was attributed to tamponade due to hemopericardium. Four of their patients had hypertension, seven were men and three, women; the youngest was 51 years and the oldest, 80 years, the average age being 65.7 years. Five of the patients were inadequately treated in relation to bed rest. In eight instances the anterior descending branch of the left coronary artery was acutely occluded, and the circumflex branch in

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two. Death was sudden in every instance, occurring two to ten days after the onset of the infarction. In 1944, also, Jetter and White⁵ reported a series of twenty-two cases of fresh myocardial infarction occurring among inmates of a mental institution. Sixteen (72.7 per cent) died from tamponade following rupture of the heart. Ten were men and 6, women; the youngest was 48 years and the oldest, 83 years, the average age being 66.5 years. Fourteen (87.5 per cent) had had hypertension, and only one complained of anginal pain. Ten were ambulatory, four had partial bed rest, and only two were in bed for the last twelve hours of their lives. The clinical diagnosis of myocardial infarction was missed in every case. The location of the infarct through which the rupture occurred was as follows: anterior wall of left ventricle in five, the posterior wall in two, and the lateral wall in one instance. Both the left ventricular wall and the interventricular septum were sites of infarcts in seven cases, while in one, both ventricles and interventricular septum were similarly affected. Presumably, death occurred within the first two weeks after onset of infarction in fourteen cases, and within three weeks in two cases. These authors failed to discover a single case of cardiac rupture among twenty-five cases of healed myocardial infarcts studied in the same institution.

Rupture of the interventricular septum following myocardial infarction is of rarer occurrence. Latham⁶ reported the first case in 1845. In 1934, Sager⁷ was able to collect eighteen cases from the literature. In 1942, there were thirty-four cases on record, and until 1943, only one more case had been added; only five cases had been diagnosed ante mortem. Recently, Master and Russell⁹ have reported a case of interventricular septal rupture following acute myocardial infarction complicated by obstruction of the superior vena cava which they were able to diagnose ante mortem.

MATERIAL

Among 1,250 autopsies performed at the Louisville General Hospital during the last five years (1939 to 1944), a total of 147 cases presented myocardial infarction. Of these, ninety-four were old infarcts and fifty-three were fresh infarcts. Of the cases of recent infarction, five died from rupture of the heart. None of the hearts presenting chronic infarction had ruptured. In four, there was perforation of the left ventricle, and in one, rupture of the interventricular septum. Thus, 9.5 per cent of the cases with recent infarction died from rupture of the heart. All the cases that presented perforation of the left ventricle died from tamponade following hemopericardium.

CASE REPORTS

CASE 1.—M. C., a 74-year-old white housewife was first seen in the Medical Clinics of the Louisville General Hospital on April 24, 1941. At that time she complained of dyspnea on exertion, headaches, and dizzy spells. Her blood pressure was 200/100. Urinalysis revealed a specific gravity of 1.009 and a trace of albumin. Symptomatic treatment failed to change her blood pressure, and her original complaints intensified. On March 11, 1944, she developed nausea and vomiting and severe dizziness accompanied by unquenchable thirst. Two days later, she developed a severe pain in the precordium, accompanied by dyspnea which required hospitali-

zation on March 14, 1944. Her past and family histories were essentially negative except for evident memory changes during the past three years.

On admission she had a temperature of 101° F., a pulse rate of 140 per minute, and a blood pressure of 182/102. Moist râles were heard over both lung bases and her heart was enlarged to the left and down. A systolic murmur was heard in all valve areas. The physical exploration was negative otherwise. Blood studies on admission revealed a white cell count of 14,500, with 80 per cent polymorphonuclear leucocytes, and the sedimentation of erythrocytes was markedly hastened. Examination of the urine showed a moderate amount of albumin and a specific gravity of 1.005.

In spite of absolute rest in bed and medication with aminophylline and papaverine in proper doses, her temperature increased to 103° Fahrenheit. On March 15, 1944, while talking to the nurse, she was taken with severe pain in the precordium and became cyanotic, raised her arms, and died.

Necropsy: On opening the chest cavity, the pericardial sac was found to be bulging with 160 c.c. of liquid blood and 240 Gm. of clot. After removal of the pericardial contents, the heart weighed 350 grams. Just to the left of the anterior interventricular sulcus, near the apex, a jagged, longitudinal slit in the epicardium measuring 3 cm. in length and surrounded by an ecchymotic area was observed. Exploration with a blunt probe demonstrated that the underlying myocardium was undermined for a distance of 1 cm. in all directions, and that there were several circuitous tracts connecting the left ventricular cavity with the outside. A blood clot measuring 2 cm. in length was occluding the circumflex branch of the left coronary artery. Severe sclerosis, with partial or complete occlusion, was observed in all the coronary vessels. Multiple myocardial scars throughout and one large fresh infarct at the point of rupture were demonstrated. There were several fresh infarcts in both lungs, and there was evidence of marked nephrosclerosis.

CASE 2.—M. V., a 78-year-old white widow, was first seen in the Louisville General Hospital, on Aug. 1, 1937, with remnants of a left-sided hemiplegia which occurred in December, 1936. At the time of admission, she complained of headaches and dizzy spells. Her blood pressure was 190/110. Her heart was enlarged to the left on percussion. She was treated symptomatically in the Medical Clinics for three years with little, if any, improvement. On June 26, 1939, she was admitted to the hospital in a critical state of shock. Six days before she had felt below par, had had dyspnea, and went to bed. At about 3:30 A. M. on the day of admission, she awakened her daughter with a cry. On arrival at the hospital she was gasping for breath, her pulse was not felt, and the blood pressure could not be measured. In spite of strenuous measures, she died at 5:40 A. M.

Necropsy: The pericardial cavity was filled with a layer of coagulated blood measuring 2 cm. in thickness. After removal of the clot, two areas of hemorrhage, one measuring 2 cm. and the other 0.5 cm. in diameter, were observed in the posterior aspect of the left ventricular wall. On further exploration, in the center of the ecchymotic areas two perforations were seen which were found to join at some depth in the wall and to form a single sinus, which opened into the cavity of the left ventricle, near the apex, where a jagged tear was visible. Practically two-thirds of the posterior wall of the left ventricle was necrotic and hemorrhagic. The remainder of the myocardium of the left ventricle was studded with scars, many of these being quite large. The coronary arteries were markedly sclerosed, and the left circumflex branch was completely occluded by a thrombus.

CASE 3.—Z. C., a 51-year-old white widow, was admitted to the Louisville General Hospital on Jan. 22, 1943. She stated that for the last five days she had been feeling dizzy, and that forty hours previous to admission, while sitting on a chair, she had been seized with a very severe stabbing pain in the precordium, radiating down her arms, and extreme dyspnea. She had no previous history of anginal pain.

On examination, the pain was continuous, the dyspnea intense, and she was vomiting profusely. Her blood pressure was 140/110; temperature, 98.4° F.; pulse rate, 120; and the respirations, 32 per minute. Moist râles were heard over both lung bases, and the heart was enlarged

to the left and down, and the sounds were distant with occasional extrasystoles. She was given morphine sulfate and atropine, the pain subsided, and she felt more comfortable.

On admission, a white blood count showed 9,000 cells per mm., of which 78 per cent were polymorphonuclear leucocytes. The erythrocyte sedimentation rate was hastened. An electrocardiogram demonstrated bundle branch block and changes suggesting a fresh infarct in the anterior surface of the left ventricle.

On Jan. 23, 1943, she complained of "fluttering of the heart," and was very anxious. The skin was moist and clammy and her heart was very irregular, the rate being about 172 per minute. Later in the day her pulse was 190 per minute, and her blood pressure was 78/62. Digitalis was administered intravenously, and she responded fairly well. On Feb. 2, 1943, her temperature was 101° Fahrenheit. She complained of annoying pains in the precordium and her blood pressure was 104/66. On Feb. 4, 1943, she suddenly developed extreme dyspnea and cyanosis, and died within a few seconds.

Necropsy: The pericardial cavity was filled with liquid and coagulated blood, part of which was beginning to organize. The heart weighed 400 grams. On the anterior surface of the left ventricle, near the apex, a fresh infarct 2.5 cm. in diameter was found which involved part of the interventricular septum. The infarcted area was very soft, and a tear about 5 mm. in length was seen extending by circuitous sinuses into the interior of the left ventricle. About 2.5 cm. from its origin a clot was found occluding the anterior descending branch of the left coronary artery. There was severe sclerosis of the other coronary arteries, with a reduction of their lumina, but no old infarcts were observed. The affected portion of the interventricular septum was so soft that dull probes could be passed through it without difficulty.

CASE 4.—A. McF., a 63-year-old white woman, was first seen in the clinics of the Louisville General Hospital on Jan. 10, 1941, complaining of dyspnea and orthopnea of three years' duration. The blood pressure at that time was 150/94 and her extremities were moderately edematous. On Aug. 7, 1942, she complained of pain in the back and abdomen, as well as of dizzy spells. At that time she presented some enlargement of the heart and her blood pressure was 170/90. On June 28, 1943, she was admitted to the hospital because of pain in the abdomen, vomiting and constipation, and severe dyspnea and orthopnea. On physical examination, her blood pressure was 170/90, her temperature was 100° F., pulse rate, 100, and respirations, 26 per minute. Her symptomatology suggested a low intestinal obstruction, and she was transferred to the surgical wards on June 29, 1943. She was given intravenous fluids (7,000 c.c.) and treated by Wangensteen suction. On July 5, 1943, her abdomen was less distended and she felt better, but on July 8, 1943, she suddenly developed severe orthopnea, became cyanotic, and died in fifteen minutes. (She had a leucocytosis of 18,350 on the day before death, and her temperature had gone up to 103° Fahrenheit.)

Necropsy: The pericardial cavity was distended with 500 c.c. of clotted blood. On the anterior surface of the left ventricle, near the apex, a large fresh infarcted area was observed. There was a ragged tear in the epicardium measuring 8 mm. in length. This external opening communicated by multiple sinuses with the cavity of the left ventricle. A large thrombus was found to be occluding the anterior descending branch of the left coronary artery, about 2 cm. from its origin. Marked sclerosis with reduction of the lumina was seen in all the coronary arteries, and areas of myocardial scarring were visible both grossly and microscopically. Aside from the cardiac findings, there were pelvic abscesses and multiple intestinal adhesions.

CASE 5.—E. G. H., a 65-year-old white man, was admitted to the Louisville General Hospital on July 23, 1943, with a severe pain in the precordium radiating to the left arm and accompanied by intense dyspnea. He stated that for the last few years he had had similar attacks of paroxysmal precordial pain lasting from 15 to 30 minutes, and usually precipitated by exercise. On the day of admission he had had an anginal seizure which was so severe that he could not move and gasped for breath.

On examination, his temperature was 101° F.; pulse rate, 110; and respirations, 30 per minute. His blood pressure was 160/95. His heart was enlarged to the left but no murmurs were heard. A white cell count of 16,400 per c.mm. with 87 per cent polymorphonuclear leucocytes was recorded on the day of admission.

On his second hospital day, a systolic murmur was heard at the apex and third intercostal space to the left of the sternum, which increased in intensity as the hours passed. The blood pressure was 75/50 by 1:00 P. M. An electrocardiogram taken at this time showed a right axis deviation, multiple premature ventricular contractions, and changes suggesting anterior infarction of the left ventricle. At 2:10 P. M. of the same day, his systolic blood pressure was 50 mm. Hg. (the diastolic pressure could not be determined) his temperature was 104 degrees F., Cheyne-Stokes respirations were present, and his pulse rate was 20 per minute. A few minutes later, the murmur became harsher, and he died after becoming deeply cyanotic. The clinical diagnosis was anterior myocardial infarction with rupture of the interventricular septum.

Necropsy: On the anterior surface of the left ventricle near the apex, a large fresh infarct measuring 2.5 cm. in diameter was seen surrounded by an ecchymotic area which included part of the apex. A ragged hole 1 cm. in diameter was discovered in the interventricular septum about 1.5 to 2 cm. from the apex. The coronary arteries were sclerotic, with marked reduction of their lumina, but the examiner failed to discover an occluding thrombus in the anterior descending or circumflex branch of the left coronary artery. Aside from the cardiac findings, there were microscopic signs of early bronchopneumonia and benign nephrosclerosis.

ANALYSIS OF CASES

In spite of the small number of cases presented in this paper, certain significant facts deserve consideration. The incidence of rupture of the myocardium following acute myocardial infarction was 9.4 per cent. This is in agreement with the latest reports.^{3,4} The average age was 66.2 years, with variations of 51 to 78 years. All of our patients belonged to the white race. Four subjects had hypertension; from one (Case 5) no record of the blood pressure was obtained previous to admission. Two patients were not properly treated in relation to medication and bed rest. The accident occurred in the home of one (Case 2), and she was dead a few minutes after admission to the hospital. The other (Case 4) had symptoms of intestinal obstruction masking the picture of myocardial infarction; as a result treatment was not directed to the heart. In the other three cases, the treatment for myocardial infarction was propitious by all standards, and the patients died in bed while receiving proper medication. The high temperature recorded in these patients suggested severe myocardial damage, and in all but two, electrocardiographic evidence of the infarction was obtained.

The ante-mortem diagnosis of rupture of the interventricular septum in Case 5 was based upon the history which suggested acute myocardial infarction, the sudden appearance of a systolic murmur which was best heard near the cardiac apex and which increased in intensity as the hours elapsed, and the electrocardiographic findings consisting of evidence of anterior myocardial infarction and right axis deviation.

All the patients died within two to thirteen days after the onset of the myocardial infarction, with an average survival of 6.2 days. This is confirmatory of the findings of others that rupture of the heart occurs, as a rule, within ten to fourteen days after the onset of myocardial infarction.^{4,5} The period of survival after the cardiac rupture in three cases where enough information could be obtained to exactly fix the time varied between two hours and ten minutes, and two days. Evidence that death did not occur instantaneously with the perforation was obtained at autopsy. In every case of rupture of the

left ventricle, large amounts of ante-mortem clot were seen in the pericardial cavity; in Case 3, the clot was beginning to organize.

All deaths from rupture of the left ventricle could be attributed to tamponade, and in every instance a large infarct in different stages of liquefaction was observed. In three patients, an infarcted area was seen on the anterior surface of the left ventricle; in one, on the the posterior surface; and in three, there was involvement of the interventricular septum as well as the left ventricular wall. One or more points of perforation, varying in size and, as a rule, jagged, were seen in every case. These were seen on the anterior surface of the left ventricle in three instances, on the posterior surface in one, and in the interventricular septum in another. The perforation in the interventricular septum was 1.5 to 2 cm. from the cardiac apex. In four patients there was thrombosis of one of the main branches of the coronary arteries, mainly the anterior descending and the circumflex. In one instance (Case 5) there was marked narrowing of the lumina of the coronary arteries, but no thrombosis was demonstrated. In every patient marked arteriosclerosis of these vessels was observed (Table I).

COMMENT

The various causes of rupture of the wall of the heart or the interventricular septum may be either traumatic, ulcerative, or secondary to massive infarction following thrombosis or marked narrowing of the major branches of the coronary arteries. The traumatic variety of rupture is by far the most common, and results, as a rule, from stab or bullet wounds of the heart. Rupture due to ulceration is rare and is always secondary to acute bacterial endocarditis. Perforation of the interventricular septum may be congenital, as a rule occurring in the upper portion or membranous portion of the septum, in contradistinction to the acquired type which is found, as a rule, in the thicker portion near the apex of the heart.

In this paper we are dealing with the type of perforation which results from massive myocardial infarction following coronary artery occlusion. The mechanism of spontaneous rupture in these cases is not well understood. But, no doubt, liquefaction necrosis in the infarcted tissue weakens the walls of the heart to a marked degree. Rupture probably occurs during systole, perhaps following an increase in the intraventricular pressure precipitated, in the majority of occasions, by physical exertion.

It is known that the intraventricular pressure is greater in the erect than in the supine position, and that the cardiac output is increased during physical exertion. The increase in cardiac output is associated with an increase in the diastolic volume of the heart and, thus, an increase in the volume of the left ventricle at the beginning of systole. This may be contributory to the greater incidence of rupture of the myocardium following infarction among ambulatory patients than among those kept in absolute bed rest for a few weeks.

The clinical picture of cardiac rupture secondary to myocardial infarction is that of acute coronary artery occlusion with sudden death. The great majority of the cases of rupture of the ventricular wall are not diagnosed clinically.

TABLE I. RUPTURE OF THE HEART FOLLOWING MYOCARDIAL INFARCTION. ANALYSIS OF 5 CASES

PATIENT	SEX	AGE	RACE	B. P.	MANAGEMENT	E. C. G. CHANGES	PERIOD OF SURVIVAL AFTER INFARCTION (DAYS)	PERIOD OF SURVIVAL AFTER PERFORATION	TYPE OF DEATH	SITE OF PERFORATION	STATE OF BLOOD IN PERICARDIUM	CHANGES IN CORONARY ARTERIES	NUMBER OF PERFORATIONS	RECOGNIZED IN AUTOPSY
M. C.	F	74	W	High	Proper	Consistent with infarction anterior surface of left ventricle	3	?	Sudden	Anterior surface left ventricle	Clotted	Thrombosis left circumflex	1 jagged	No
M. V.	F	78	W	High	Improper	Not taken	6	2:10 minutes	Sudden	Posterior surface left ventricle	Clotted	Thrombosis left circumflex	2 jagged	No
Z. C.	F	51	W	High	Proper	Bundle branch block and infarct anterior surface left ventricle	13	2 days	Sudden	Anterior surface left ventricle	Liquid and clotted	Thrombosis anterior descending	1 small	No
A. McF.	F	63	W	High	Improper	?	7	?	Sudden	Anterior surface left ventricle	Clotted	Thrombosis anterior descending	1 jagged	No
E. G. H.	M	65	W	?	Proper	Left axis deviation; infarction anterior surface left ventricle	2	About 6 to 8 hours	Sudden	Interventricular septum	—	Arteries severely sclerotic	1 cm. diameter	Yes

The clinical diagnosis of rupture of the interventricular septum is based upon the sudden appearance of a loud systolic murmur, best heard over the fourth and fifth intercostal spaces to the left of the sternum following myocardial infarction. On occasion, a thrill can be palpated over the same areas. Furthermore, this systolic murmur becomes harsher with time. Auriculoventricular conduction defects are rarely present in this condition, and the electrocardiographic tracings show changes consistent with myocardial infarction, and right ventricular strain. The period of survival after the accident may vary from a few hours to eight months.⁸

SUMMARY AND CONCLUSIONS

1. In a series of 1,250 consecutive autopsies performed at the Louisville General Hospital during the past five years, there were 147 cases of myocardial infarction. Of these, fifty-three were acute, and ninety-four were chronic.

2. Rupture of the heart was observed in five instances. This accident occurred exclusively in patients with acute infarction. In four patients, there was rupture of the wall of the left ventricle, and in one, perforation of the interventricular septum. Thus, 9.4 per cent of the patients of this series with acute infarction died from this accident.

3. Rupture of the interventricular septum was recognized ante mortem. Diagnosis was based upon the history of severe anginal pain, the sudden appearance of a systolic murmur which rapidly increased in intensity, and the electrocardiographic evidence of myocardial infarction and right axis deviation.

4. In every instance of rupture of the left ventricle, ante-mortem clotting in the pericardial sac was observed, and in one case, this clot was beginning to organize. It is evident that in the majority of the patients of this series death did not occur instantaneously with cardiac rupture resulting from acute myocardial infarction.

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PAROXYSMAL AURICULAR TACHYCARDIA AT A RATE OF 86 PER MINUTE

REPORT OF A CASE

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DURING a paroxysm of auricular tachycardia the heart beat is usually excessively rapid, and a rate of less than 140 per minute is exceptional. Lewis¹ stated that the rate may be as low as 110 per minute. Miller and Perelman² recently reported two cases of paroxysmal auricular tachycardia with unusual response to change in posture; the rate in the supine position was as low as 100 per minute in the first case and 113 per minute in the second. Iliescu and Sebastiani³ described an interesting case in which quinidine brought about a gradual slowing of the rate of an auricular tachycardia from 158 to 83 per minute before the normal sinus mechanism was resumed at 79 per minute. In the present communication we record a case in which paroxysmal auricular tachycardia occurred spontaneously at a rate of 86 per minute. The patient was in the sitting position and no drugs had been administered.

CASE REPORT

H. H., a 39-year-old Negro woman, was referred to the clinic in November, 1945. Her present illness had begun in March, 1940, when she first complained of dyspnea on exertion, cough, expectoration, and hemoptysis. She was found to have far-advanced pulmonary tuberculosis and was sent to a sanatorium. After fifteen months of treatment, consisting of bed rest and graduated exercise, she was discharged with her disease apparently arrested. She felt quite well until shortly before she was seen at the clinic, when her original symptoms returned. On examination she appeared to be well nourished and well developed. There was pallor of the mucous membranes. The thyroid gland was not enlarged. The thorax was symmetrical in contour. Expansion of the chest was normal and there was no impairment of the percussion note. The breath sounds were diminished and scattered râles were audible throughout both lung fields. The apex beat of the heart was not displaced, no thrills or murmurs were present, and the heart sounds were normal. The heart rate was 84 per minute and the rhythm appeared to be regular. The blood pressure was 120/80. The liver and spleen were not palpable and there was no peripheral edema.

An x-ray film of the chest revealed diffuse, scattered, productive infiltrations throughout both lung fields. The heart was vertical in position, and there was marked prominence of the pulmonary artery segment. The aortic knob was poorly visualized. Repeated examinations of the sputum were consistently negative for tubercle bacilli. The blood count showed a mild normocytic anemia and a normal white blood cell and differential count. The erythrocyte sedimentation rate was 80 mm. in one hour. The blood Kline test was negative. The urine was normal.

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The patient became progressively more dyspneic on exertion, and also suffered from attacks of paroxysmal dyspnea while at rest. She died suddenly during one of these paroxysms of dyspnea of Feb. 21, 1946. The cause of death was presumed to be pulmonary insufficiency. Necropsy was not performed.

ANALYSIS OF ELECTROCARDIOGRAMS

Frequent electrocardiograms were taken. Two of these will be reported in some detail. In both instances, the patient was in the sitting position and there had been no recent drug administration. Fig. 1 illustrates the electro-

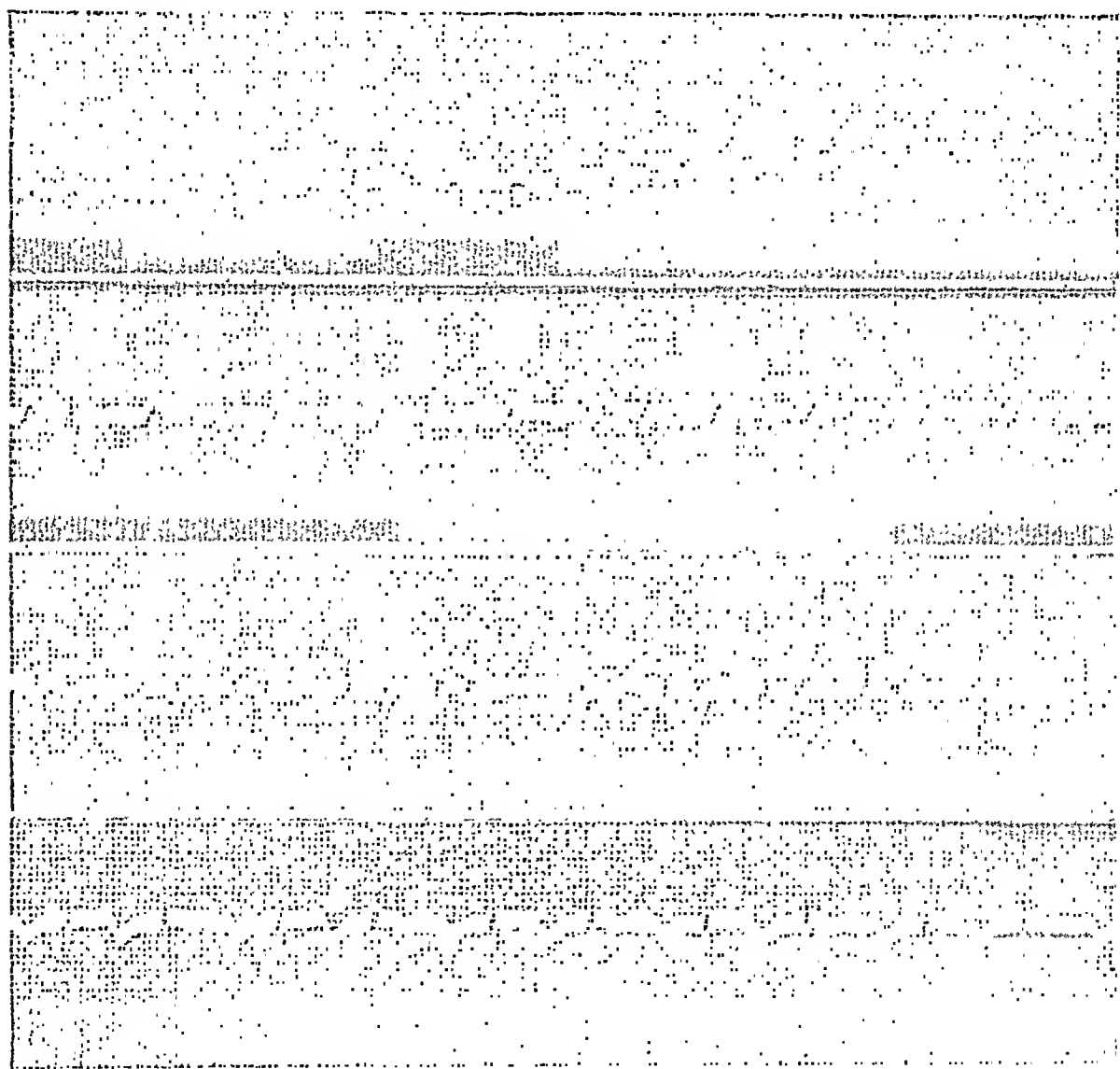


Fig. 1.—Electrocardiogram taken Nov. 29, 1945. The following auricular complexes are identified as premature auricular contractions: In Lead I, the second, fourth, sixth, eighth, and tenth. In Lead II, the eighth and tenth. In Lead III, the second, fourth, and sixth. In Lead CF_4 , the fifth, seventh, and tenth. Note sinus arrhythmia and shifting of pacemaker in S-A node.

cardiogram which was taken on Nov. 29, 1945. The dominant rhythm was of sinoauricular origin, with sinus arrhythmia and a shifting pacemaker in the sinus node. There was a tendency to right axis deviation. The P-R interval following normal sinus impulses was from 0.20 to 0.22 second in duration, and

the QRS interval measured 0.06 second. The S-T segment was slightly elevated in Lead I and depressed in Leads II and III. The T waves were inverted in Leads II, III, and CF₄. This pattern was believed to be indicative of right ventricular strain. The dominant rhythm was interrupted by frequent auricular premature contractions. A bigeminal rhythm was present in Lead I. The ectopic P waves were more sharply peaked and narrower than the normal auricular complexes, and were multifocal in origin. The P-R interval corresponding to ectopic P waves was prolonged from 0.28 to 0.34 second. The coupling between normal and ectopic beats was not fixed. The inter-extrasystolic interval was constant in Lead I, and measured 1.36 seconds. It varied slightly in the other leads, between 1.29 and 1.31 seconds.

The tracings shown in Fig. 2 were recorded on Dec. 4, 1945. In Lead II the first eight beats constituted a run of a paroxysmal auricular rhythm which terminated abruptly and was followed by a postparoxysmal pause. The interval between beats measured 0.70 second, corresponding to a rate of 86 per minute. The P waves were definitely aberrant, and were higher in voltage than the normal P waves. The P-R interval was prolonged to 0.36 second. The ninth, eleventh, and sixteenth auricular complexes were of normal sinus origin. The P-R intervals following these beats varied from 0.24 to 0.28 second. The tenth auricular beat was an isolated auricular extrasystole. The twelfth, thirteenth, fourteenth, and fifteenth auricular beats were ectopic and varied in form, indicating a shift of the ectopic pacemaker. The seventeenth and eighteenth auricular beats were of sinus nodal origin, but outside of the normal pacemaker. The P-R intervals of the latter two beats were 0.22 and 0.24 second, respectively. It will be noticed that the intervals between the eighth and tenth, and the tenth and twelfth P waves were twice that of the shorter inter-extrasystolic interval. In Lead III, also, a short run of auricular extrasystoles occurred at the beginning of the tracing. This run consisted of six beats. Following a postparoxysmal pause, the normal sinus mechanism was resumed at a rate of about 70 per minute, with shifting of the pacemaker in the sinus node. The eleventh and seventeenth auricular beats were extrasystoles. It is of particular interest that the interval between the sixth and seventeenth auricular beats was an almost exact multiple of the shorter inter-extrasystolic intervals.

Electrocardiograms which were taken on other occasions consistently showed frequent premature auricular contractions. The P-R interval of normal beats was from 0.20 to 0.26 second, while that of the premature beats varied from 0.28 to 0.36 second.

The ectopic P waves could be differentiated definitely from nomotopic beats due to the following facts: (1) They were quite markedly aberrant. (2) In Lead II the voltage of some of the ectopic beats was higher than that of the normal sinus beats. If the pacemaker were dislocated from its normal position to one lower in the S-A node, the P wave should decrease in voltage. (3) The P-R interval of ectopic beats was much longer than that of the normal sinus beats. Again, with a shift in the pacemaker in the sinus node, a P-R interval that was normal, or shorter than normal, should be anticipated.

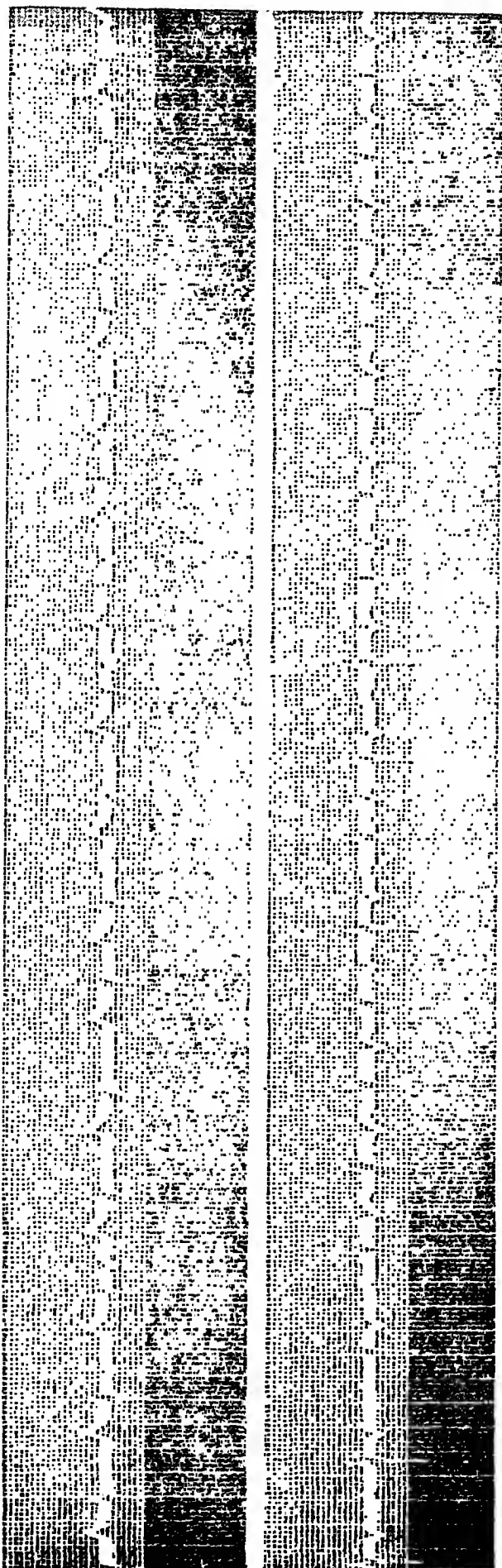


Fig. 2.—Electrocardiogram taken Dec. 4, 1945, Leads II and III. Discussed in text.

The runs of extrasystoles which are shown in Fig. 2 fulfilled the following criteria for the diagnosis of paroxysmal auricular tachycardia: (1) the P waves were definitely aberrant, (2) the first beat of the paroxysm was premature, (3) the last beat was followed by a postparoxysmal pause, and (4) the rhythm during the paroxysm was perfectly regular. The rate of the paroxysm, however, did not fall within the tachycardiac range since it was only 86 per minute. It was, nevertheless, faster than the rate of the normal sinus rhythm which, at the time, was only 70 per minute.

DISCUSSION

Two main theories have been advanced as a possible explanation for the mechanism of paroxysmal auricular tachycardia, namely re-entry and parasystole. Movitt⁴ stated that auricular tachycardia probably is not due to a higher center of rhythmicity since, if such were the case, rhythms would be observed with rates from 90 per minute and up. He stated further that most authorities regard auricular tachycardia as due to the re-entry phenomenon. Lewis,⁵ however, pointed out that the main objection to the re-entry theory is the presence of an isoelectric interval between auricular beats. Barker, Wilson, Johnston, and Wishart⁶ countered this objection with the hypothesis that the re-entrant wave involved in part of its pathway either the S-A or A-V node; the impulse would be delayed in traversing nodal tissue and during this interval would not cause a deflection in the electrocardiogram. In paroxysmal tachycardias at low rates of speed, however, the isoelectric interval would be too prolonged to accommodate this mechanism. We agree with the contention of Iliescu and Sebastiani³ that, in their case, a rate of a paroxysmal auricular tachycardia of only 83 per minute made the re-entry theory untenable, and the same applies to our case.

In parasystole, ectopic beats occur at intervals which bear no fixed relationship to the normal sinus rhythm but have a regular, inherent rhythm of their own, so that the interval between extrasystolic beats is an exact, or nearly exact, multiple of a least common denominator. These criteria were fulfilled in our case. As can be seen in Fig. 2, the longer inter-extrasystolic intervals were almost exact multiples of the shorter intervals between beats during runs of tachycardia.

If the theory of parasystole be applicable to an auricular rhythm, the assumption must follow that an impulse can arise, *de novo*, from auricular tissue, a fact which is not generally accepted. Whether the auricle possesses a specific conduction system is unknown. Since it is doubted that an impulse can arise outside of the specific system, the explanation proposed for ectopic auricular rhythms is that they originate in rests of sinus nodal tissue scattered throughout the mass of nonspecialized auricular muscle.⁷ If this hypothesis indeed be true, then it would be logical to expect that these aberrant rests potentially, at least, should possess the same properties as other portions of the specific system.

Centers of automaticity throughout the specific conduction system of the heart possess the potentiality of developing rhythms of varying rates of speed.

Rhythms of nomotopic origin may vary from a sinus bradycardia of as low a rate as 35 per minute through the range of normal sinus rhythm and into the fast rates of a sinus tachycardia, reaching levels up to 200 or more per minute. The lower centers of impulse formation, the junctional tissue and the ventricular conduction system, do not have the marked lability of the sinus node, but do give rise to rhythms of either very slow or very rapid rates, and, more rarely, intermediate rates which exceed the rate of the sinus pacemaker at the moment. Thus, A-V nodal rhythms are usually characterized by rates of 40 to 50 per minute and A-V nodal tachycardias by rates of 160 to 250 per minute. In the intermediate zone, rates of from 60 to 100 or more per minute may occur, and if this rate exceeds that of the sinus nodal pacemaker, A-V nodal interference dissociation may result. Similarly, still lower centers in the His bundle or bundle branches may exhibit the same phenomenon, giving rise to idioventricular rhythm, paroxysmal ventricular tachycardia, or interference dissociation.

The case which we have described exhibited an ectopic auricular rhythm which was faster than the normal sinus rhythm at the time and, therefore, took control of the heart, but yet was at a subtachycardiac level (that is, the rate was only 86 per minute). We believe that this type of rhythm is analogous to A-V nodal or ventricular rhythms of intermediate rates of speed, as seen in interference dissociation.

SUMMARY

1. An unusual auricular rhythm is described. It fulfilled the major criteria for the identification of paroxysmal auricular tachycardia, with the exception of the fact that the rate was comparatively slow at 86 per minute. The rate of the normal sinus rhythm at the time, however, was only 70 per minute.

2. Theoretical implications are discussed, and it was concluded that the underlying mechanism of this arrhythmia was parasystole.

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WOLFF-PARKINSON-WHITE SYNDROME IN A CASE OF CONGENITAL HEART DISEASE

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THE majority of cases of the Wolff-Parkinson-White syndrome reported in the literature have been normal young adults with no demonstrable organic heart disease. In his review of the literature on the subject, Bishop¹ studied forty-five cases, and found a few patients who had acute glomerulonephritis, inactive rheumatic heart disease, and hypertensive cardiovascular disease associated with the syndrome under discussion. None of the cases in this series had congenital heart disease. Bishop concluded that when organic heart disease was present, it was only coincidental, and not responsible for the syndrome of a short P-R interval and widened QRS complex of the bundle branch block type.

Two possible explanations for the conduction disturbance of the Wolff-Parkinson-White syndrome can be stated. It is a functional or a structural anomalous disturbance.

Butterworth and Poindexter² have experimented with cats and dogs by the use of an artificial electrical conducting pathway and were able to reproduce the pattern of the Wolff-Parkinson-White syndrome electrocardiographically. This evidence would be in favor of the explanation which attributes the syndrome to an anomalous structural disturbance. Wood, Wolferth, and Geckeler³ have given additional evidence in favor of this view. They reported a case of short P-R interval and prolonged QRS complex in a 13-year-old boy who died during an attack of paroxysmal tachycardia. The autopsy findings demonstrated accessory muscular connections between the right auricle and right ventricle, in the same general region as the ones described by Kent.

On the other hand, Fox, Travell, and Molofsky⁴ described a case in a 20-year-old man, in whom they were able to widen the QRS interval with digitalis and shorten it with atropine. They, therefore, assumed that there was a vagal component in the mechanism of the Wolff-Parkinson-White syndrome.

Recently, the author⁵ reported a case in which an electrocardiogram showed alternation of normal complexes and complexes characteristic of the Wolff-Parkinson-White syndrome. It was felt that alternate conduction of auricular impulses through the bundle of His and through an aberrant auriculoventricular pathway, such as the bundle of Kent, would best explain this finding.

Since any observation which bears any relationship to the etiological explanation of the Wolff-Parkinson-White syndrome is of interest, the following case is being reported.

CASE REPORT

A 27-year-old soldier with three years and eight months service was admitted to the Regional Hospital at Fort Leonard Wood, Mo., on Oct. 12, 1945, after a routine physical examination for separation had revealed that he had tachycardia, clubbing of the fingers, and an enlarged heart.

His past history and family history were noncontributory. He did not have any knowledge of heart disease, having led an active life and engaged in combat in the European Theatre of Operations with a field artillery unit. There was no history of shortness of breath, precordial pain, nor any other distress. There was no history of rheumatic fever nor chorea in the past. His face and hands always were ruddy, but he considered this to be a normal condition.

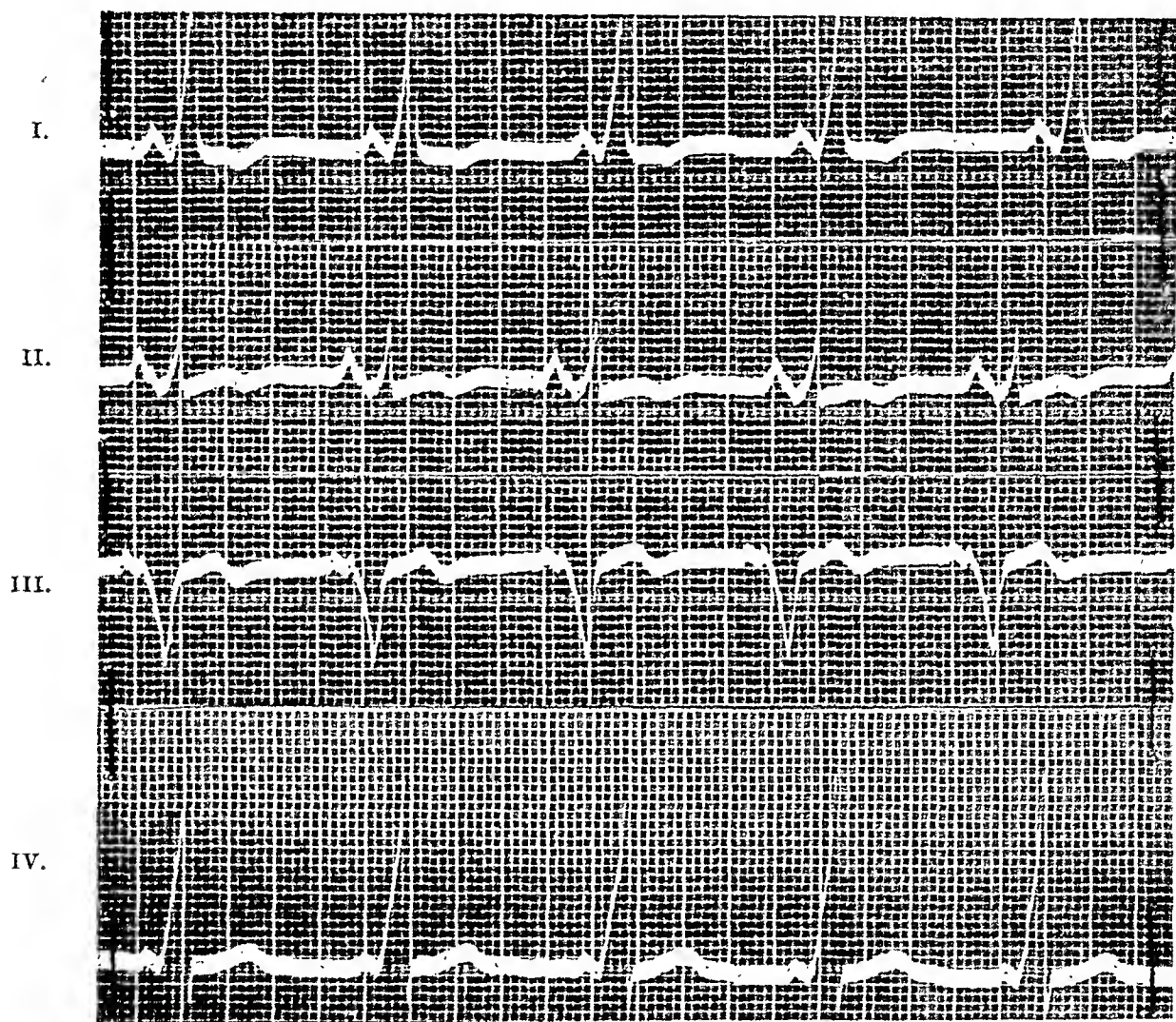


Fig. 1.—Electrocardiogram showing Wolff-Parkinson-White syndrome taken Oct. 12, 1945.

On physical examination, his face and neck were of a ruddy complexion. Both hands and feet showed definite cyanosis in the dependent position. There was a moderate clubbing of the fingers and toes. The heart rate was 78 per minute, and the blood pressure was 128/82 in the right arm and 124/82 in the left arm. There was a loud systolic murmur along the left sternal border, followed by a reduplicated second heart sound. The cardiac murmur was loudest between the third and fourth left intercostal spaces in the recumbent and left lateral position.

The electrocardiogram taken on Oct. 12, 1945, showed the pattern of the Wolff-Parkinson-White syndrome and was unchanged each time it was repeated (Fig. 1). Atropine and exercise had no effect on the tracing. An x-ray film of the heart showed unusually well-rounded contours

with enlargement. The transverse diameter of the heart was 16 cm. and that of the chest was 29.5 centimeters (Fig. 2).

Blood Kahn was negative. Blood count showed 5,530,000 erythrocytes; hemoglobin, 109 per cent (17.0 Gm.); and 10,000 white blood cells, with 71 per cent polymorphonuclear leucocytes, 27 per cent lymphocytes, 1 per cent eosinophiles, and 1 per cent basophiles. Blood sedimentation



Fig. 2.—Teleroentgenogram of heart made Oct. 12, 1945.

rate (Westergren) was 3 mm. in one hour. The hematocrit showed 56 per cent volume of packed red blood cells. Urine was negative.

The ether circulation time was performed on two separate occasions, several days apart, and a double end point was found each time. It was found to be 3 and 7 seconds the first time, and 5 and 9 seconds on the recheck test.

COMMENT

The diagnosis of congenital heart disease seemed to be warranted because of the cardiac murmur, x-ray findings, clubbing of the fingers, cyanosis, and double end point in the ether circulation time. The anatomic lesions present in this case were considered as possibly a patent interventricular septum, slight dextroposition of the aorta, and slight hypertrophy of the right ventricle.

It is entirely realized that the occurrence of the Wolff-Parkinson-White syndrome in a single case of congenital heart disease constitutes no real evidence of the congenital origin of this disturbance. It is felt, nevertheless, that the association as it existed in the case reported is of interest.

SUMMARY

1. A brief resume of some of the etiological factors in the Wolff-Parkinson-White syndrome has been presented.
2. A case is presented in which congenital heart disease was associated with this syndrome.

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Abstracts and Reviews

Selected Abstracts

Vaughn, A. M.: Multiple Retrograde Saphenous Vein Ligation and Phlebectomy With Aid of Malleable Intraluminal Guide. Surgery 21:851 (June), 1947.

In an attempt to counteract the tendency for recurrences of varicosities and the symptoms of chemical phlebitis which follow the use of a sclerosing solution after ligation of the saphenous vein, the author utilized a procedure involving high saphenous vein ligation combined with multiple retrograde ligation and excision of segments of vein. To overcome the difficulty of locating the saphenous vein above the knee, he inserted a flexible uterine probe into the lumen of the vessel near the fossa ovalis and passed it downward. With the guide in the vein, the vessel can be palpated easily through the subcutaneous tissue and thus exposed, dissected out, and a segment removed. The guide was also utilized in locating and ligating incompetent communicating vessels. It was the author's impression that recurrences still occurred with such a procedure, but that they were not as frequent as when ligation and retrograde injection were used.

ABRAMSON.

Comroe, J. H., Jr., and Botelho, S.: The Unreliability of Cyanosis in the Recognition of Arterial Anoxemia. Am. J. M. Sc. 214:1 (July), 1947.

Despite the two careful studies by Stadie and by Lundsgaard and Van Slyke which had indicated some years ago that serious arterial anoxemia may exist before even moderate cyanosis is visible, most physicians have continued to regard cyanosis as the most characteristic sign of anoxemia and the most reliable guide for intelligent oxygen therapy. The development of the oximeter by Millikan provided the authors with a new method with which they could repeat and extend earlier studies, which had given the impression that excellent diagnosticians differ widely in their ability to recognize visually the presence of arterial anoxemia. It was found that the majority of 127 observers were unable to detect the presence of definite cyanosis until the arterial oxygen saturation fell to approximately 80 per cent; 25 per cent of observers did not note definite cyanosis even at arterial saturation levels of 71 to 75 per cent. There were marked variations in the ability of an observer to note cyanosis in different subjects or even in the same subject at different times. There were wide variations in color estimations when five to ten observers watched cyanosis develop in the same subject at the same time.

It is concluded that the detection of cyanosis is dependent not only upon variable factors in the patient but also upon the ability of individual observers to note color changes. Visual impressions of cyanosis are unreliable. Serious grades of arterial anoxemia may be unrecognized by many physicians unless arterial blood is obtained and analyzed for oxygen content and capacity.

DURANT.

Katz, S., Hussey, H. H., and Veal, J. R.: Phlebography for the Study of Obstruction of the Veins of the Superior Vena Caval System. Am. J. M. Sc. 214:7 (July), 1947.

Phlebography, by providing roentgen visualization of the veins, offers a method unequalled by other techniques for defining and localizing lesions of the veins and determining the distribution of the collateral circulation. This method has been used mainly in connection with thrombosis

of the veins of the lower extremities. Its importance in similar lesions of the veins of the superior vena caval system has not been emphasized. It provides anatomic details which otherwise could be obtained only by dissection. For example, there is no other means to differentiate clinically obstruction of both innominate veins from occlusion of the superior vena cava, or axillary vein thrombosis from obstruction of the subclavian. There is no more accurate method for study of the development and extent of the collateral venous circulation. Simplicity is one of the features which adds to the attractiveness of the method, and it is almost entirely safe. The interpretation of the roentgenograms requires merely a superficial knowledge of anatomy; there is nothing like the difficulty encountered in attempts to interpret phlebograms of the deep veins of the leg in which anatomic variation is frequent and ideal visualization difficult to obtain. An error of interpretation may occur when the film is exposed too soon in which case there will appear to be an abrupt termination of the dye-filled veins, simulating obstruction. When there is doubt on this score, the phlebogram must be repeated, using a larger amount of the contrast medium so that the film can be made after a longer interval of time from the start of the injection.

It is desirable to have venous pressure measurements made in conjunction with a phlebographic study. When there is obstruction in the veins of the superior vena caval system, the venous pressure usually is abnormally high and rises higher with the "exercise test." It is often found that with the development of a collateral circulation the venous pressure becomes lower and may even become normal, although the response to the "exercise test" persists. This indicates functional improvement of the venous circulation, a fact which is not apparent from the phlebographic study alone.

DURANT.

Heyer, H. E., Winans, H. M., and Plessinger, V. I.: Alterations in the Form of the Electrocardiogram in Patients With Mental Disease. Am. J. M. Sc. 214:23 (July), 1947.

In a series of 200 patients with mental disease, a high incidence of electrocardiographic aberrations was noted as compared with 200 normal subjects. Definite changes were noted in 21.5 per cent of the psychiatric patients, as compared with a frequency of only 3 per cent of such changes in the normal subjects. The similarity of many of these changes to those produced by emotional stimuli, and by artificial means of stimulation of the autonomic nervous system, is discussed. The need for caution in interpreting such findings as abnormal, when they are seen in mentally ill patients or in normal persons who are temporarily emotionally disturbed, is pointed out.

DURANT.

Alexander, F., and White, P. D.: Four Important Congenital Cardiac Conditions Causing Cyanosis To Be Differentiated From the Tetralogy of Fallot: Tricuspid Atresia, Eisenmenger's Complex, Transposition of the Great Vessels, and a Single Ventricle. Ann. Int. Med. 27:64 (July), 1947.

The clinical, laboratory, and embryologic features of the four types of cyanotic congenital cardiac disease mentioned in the title of the paper are briefly reviewed. In the case of tricuspid atresia, the Blalock operation was performed; and although the cyanosis was immediately improved by this procedure, the 5½-month-old infant died suddenly seven and one-half hours postoperatively. At autopsy the tricuspid valve was undeveloped, and anatomic adaptations consisting of interatrial and interventricular septal defects were present. The 17-year-old patient, with transposition of the great vessels was also operated upon for the purpose of performing a Blalock procedure, but this plan was abandoned when the anomaly of the great vessels was found. This patient also died suddenly seven and one-half hours postoperatively. At autopsy the only anatomic adaptation consisted of a patent foramen ovale. The 1-month-old infant with the common ventricle (cor biloculare) was extremely ill throughout the four day hospitalization prior to his sudden death from circulatory and respiratory failure. The anatomic diagnosis was established at the autopsy table. Angiocardiography or intracardiac catheterization was not used in any of the cases reported in this paper.

WENDKOS.

Hecht, H. H.: Heart Trauma: Myocardial Involvement (Contusion) Following a Non-penetrating Injury to the Chest (Airplane Accident). *Ann. Int. Med.* 27:126 (July), 1947.

A 34-year-old civilian air pilot had always been in good health prior to a severe chest injury which he suffered when he was violently pulled forward against the resistance of his safety belt during a plane crash. When admitted to the hospital, he was in shock and roentgenograms revealed fractures of the left fifth and sixth ribs, the right sixth and tenth ribs, the sacrum, the transverse processes of the fifth lumbar vertebra, the right radius and ulna, and the left tibia and fibula. There was a small collection of fluid in both pleural cavities. Shock was treated with plasma, blood transfusion, and intravenous glucose and saline; with this therapy, the blood pressure rose from 90/60 to 110/70 and his shock state disappeared.

Examination of the heart at the time of admission revealed no abnormalities. Twenty-four hours after the injury, he received an injection of 10 c.c. of adrenal cortical extract which was followed two hours later by the development of cyanosis, severe dyspnea, and diaphoresis. The heart sounds during this episode of respiratory distress were muffled and the pulse rate had increased to 145 per minute. Within several hours he was again comfortable but the following morning the examiner noted a persistent tachycardia and an apical protodiastolic gallop rhythm. Because of the persistence of the gallop rhythm and the tachycardia, even on the fourth hospital day, an electrocardiogram was made. This was found to be normal. Seven days following the injury another electrocardiogram was made and minor T wave changes in the unipolar precordial leads derived from Position 1 to Position 5 were noted. Electrocardiograms on succeeding days showed a progressive distortion of the T waves in these same leads and sixteen days after the accident, this deflection remained negative in precordial leads derived from Positions 1, 2, and 3. He was discharged from the hospital twenty days after the accident, since he seemed to have made a good clinical recovery. When seen six months later he was quite well except for nonunion of the fractured left wrist. The electrocardiogram made at the time of this follow-up visit was entirely normal.

The clinical findings and the temporary T-wave changes in the precordial leads are interpreted by the author as manifestations of contusion to the superficial layers of the myocardium close to the interventricular septum. He does not completely discard the diagnosis of a traumatic pericarditis. The possibility that the cardiac complications and the T-wave changes were causally related to the injection of adrenal cortical extract is dismissed by the author.

WENDKOS.

Cavelti, Philip A.: Studies on the Pathogenesis of Rheumatic Fever. I: Experimental Production of Autoantibodies to Heart, Skeletal Muscle and Connective Tissue. *Arch. Path.* 44:1 (July), 1947.

The author previously developed "autoantibodies" to kidney tissue in rabbits and rats by injecting renal material in combination with bacterial substances, producing at the same time a glomerulonephritis. He then investigated the ability of streptococci to render other tissues antigenic, especially heart muscle, skeletal muscle, and connective tissue; structures that are chiefly damaged in rheumatic fever.

Group A beta hemolytic streptococci were the source of the streptococcic protein which was emulsified, mixed with emulsions of ground tissues from rats, and injected into other rats intraperitoneally on ten successive days. This schedule was repeated as often as six times at monthly intervals.

Serologic tests on the blood of these rats showed the presence of antibodies (high agglutination titer) when their serums reacted in vitro with extracts of plain (untreated) homologous tissues. These autoantibodies reached their highest titer on the seventh day after the last injection, but they were present to some degree many weeks after immunization. Control serums from normal untreated rats and from rats treated with streptococci alone and with tissue emulsion alone were also tested. All control serums were negative. Serums from rats treated with the streptococcus-tissue emulsion showed true specificity of the autoantibodies when they failed to react with heterologous tissue extracts, such as liver, kidney, or spleen.

Cavelti concluded that the streptococcus has the capacity of rendering certain substances of animal tissues antigenic for the homologous species, presumably by some loose combination between the streptococcus and the tissue substance. The antibodies formed in response can react with tissue component alone (without the presence of streptococci). Such antibodies may be designated as isoantibodies, and since they can cause damage in the same animal in vivo, the term "autoantibody" is applicable.

GOULEY.

Aronson, S. F., and Leroy, E.: Electrocardiographic Findings in Leukemia. *Blood*. 2:356 (July), 1947.

The authors review eight cases of leukemia in an endeavor to determine the electrocardiographic findings in this disease. In five patients, electrocardiograms were taken less than one month before death, and in the three other patients, five weeks, two months, and seven months, respectively, before their death.

Post-mortem examination was performed on all of the eight patients. In four of them, leukemic infiltrates were noted in the various layers of the heart and particularly in the myocardium. These patients were among the five who presented signs of cardiac failure. In the other four patients, the small vessels of the myocardium were engorged with immature white cells. In two instances this capillary engorgement was associated with recent small foci of interstitial hemorrhages. Severe fatty degeneration was noted in one patient of this group, who manifested clinical evidence of left heart failure.

The electrocardiographic changes consisted of sinus tachycardia, S-T segment depression, T-wave inversion in limb and precordial leads, prolongation of the PR interval, and premature contractions.

The authors believe that there is a close correlation between the presence of leukemia, myocardial infiltration, signs of heart disease, and abnormalities of the electrocardiogram.

BELLET.

Koenig, A., and Young, E. W.: The Sedimentation Rate in Myocardial Infarction. *Pennsylvania M. J.* 50:1060 (July), 1947.

The authors studied the sedimentation curves in twenty-one cases of coronary occlusion with myocardial infarction. They used a Cutler tube in a Linzenmeier rack with a column of blood 50 mm. long, and readings of the height of the red cell column were made every five minutes for one hour. The normal rate of sedimentation by this method is generally considered to be 1 to 8 mm. in one hour for men and 1 to 10 mm. in one hour for women.

They found that the acceleration of sedimentation begins in the first hours after the thrombotic lesion occurs. The most rapid phase appears four or five days after the acute attack, and is characterized not only by a fall of 20 or 25 mm. in an hour, but also by the beginning of sedimentation in the second or even the first five-minute period. A curve of equal depth which does not begin to fall until the third or fourth five-minute period indicates either the preliminary acute phase, or the beginning of improvement. These authors believe that improvement in the sedimentation curve is a prerequisite for allowing the patient to leave his bed.

Two cases are present in which definite acceleration persisted for periods of two to six months after the acute attack.

BELLET.

Neuhof, H.: Venous Thrombosis and Peripheral Pulmonary Embolization. Part I. Diagnosis of Venous Thrombosis in the Lower Extremities. *J. Mt. Sinai Hosp.* 14:110 (July-August), 1947.

In the diagnosis of venous thrombosis of the lower extremities, the author presents the commonly described signs and also calls attention to a finding which is apparently not generally known, namely, infiltration felt on palpation of the deep calf musculature. The area of infiltration, which corresponds to the general region of the deep veins of the calf, is determined by having the patient rest his heels on the bed, flex the knees, and relax the calf muscles. Thickening and

infiltration deep to the gastrocnemius and tenderness are considered a positive sign. This finding may exist in venous thrombosis even when Homan's sign is negative. The author also believes that records of the circumference of the calf should be obtained routinely on every patient at the beginning of bed illness. In this manner an increase due to venous thrombosis can more readily be determined.

The author points out that venography cannot be depended upon to make the diagnosis of deep thrombophlebitis and that it is of decisive diagnostic value only if a normal venous pattern has been revealed and thus the absence of venous thrombosis established. He describes a modification of the Bauer technique which involves the injection of an additional 20 c.c. of diodrast followed by further x-rays of the thigh and leg. This procedure produces better visualization of the femoral and iliac veins than is obtained with the original method. The author believes that the most important indication for femoroiliac venography exists in the case of the patient who has suffered a severe pulmonary embolism and in whom there is no clinical lead as to whether or not the embolus is derived from the legs. It is also useful in instances in which the diagnosis of thrombosis cannot be made clinically.

ABRAMSON.

Bachr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma. J. A. M. A. 134:1169 (Aug. 2), 1947.

In 1942, Klemperer and the authors employed the term "diffuse collagen disease" to indicate that in disseminated lupus erythematosus and in diffuse scleroderma, the basic morphologic changes were found in the connective tissues. Similar but less conspicuous changes in the connective tissues are observed also in rheumatic fever, periarteritis nodosa, rheumatoid arthritis, thromboangiitis obliterans, and serum sickness. The following report is a reiteration and amplification of their views on the subject. One important purpose of this report is to emphasize that the allergic basis for this condition is far from proven.

Connective tissue can react to injury in three basic ways: by fibrinoid degeneration or necrosis, by fibrillar augmentation or sclerosis, by cellular proliferation, or by a combination of these changes. Fibrinoid degeneration of collagen can occur both as a general or as a local expression of injury in a variety of heterogeneous and dissimilar disease processes. Fibrinoid degeneration of collagen is, therefore, not a pathologic process of sufficient specificity to serve as a reliable common denominator for the classification of disease. It certainly does not warrant the grouping of all such conditions into a common category of allergic diseases.

Disseminated lupus erythematosus and diffuse scleroderma have in common a similar morphologic expression, namely, fibrinoid degeneration of collagen and identical lesions of blood vessels, glomeruli, endocardium, and the serous and synovial membranes. However, they are so dissimilar clinically that they seem related neither to each other nor to rheumatic fever, rheumatoid arthritis, serum sickness, periarteritis nodosa, or thromboangiitis obliterans, in which similar collagen changes may occur as part of the pathologic process.

Acceptance of an allergic basis for these two diseases without other supporting evidence serves merely to discourage other investigative approaches into their essential nature.

BELLET.

Martin W. B., and Spink, W. W.: Endocarditis Due to Type B Hemophilus Influenzae Involving Only the Tricuspid Valve. Am. J. M. Sc. 214:139 (August), 1947.

A case is reported of a 17-year-old girl, who had a debilitating febrile disease which produced symptoms for five months before her death. A rough systolic murmur was heard in the fourth left intercostal space, and, late in the course of the disease, a diastolic murmur was heard in the same region. The spleen became palpable during the latter part of the illness. No petechiae were observed at any time. Repeated blood cultures were sterile, except on two occasions when a coagulase negative staphylococcus was obtained. At post-mortem examination the entire length of the tricuspid valve was found to be occupied by large, yellow, warty vegetations extending a full 18 mm. out from the valve margin. The vegetations extended down the chorda tendineae and there was one patch on the ventricular endocardium. The aortic and pulmonary

valves were normal. The mitral valve showed slight thickening but was not deformed and had no vegetations. Microscopically, the mitral valve showed evidence of an old rheumatic infection which had not healed completely. A pure culture of *Hemophilus influenzae*, Type B, was isolated from the vegetations on the tricuspid valve. Inasmuch as this organism had not been found ante mortem, streptomycin therapy had not been tried.

As far as the authors can determine, this represents the first reported case of subacute bacterial endocarditis due to *Hemophilus influenzae*, Type B. It is also of special interest because of the isolated involvement of the tricuspid valve.

DURANT.

Stats, D., Neuhoof, H.: Concentrated Aqueous Heparin. A New Form of Intramuscular Administration. Am. J.M. Sc. 214:159 (Aug.), 1947.

This communication describes the clinical utilization of a new preparation of concentrated aqueous heparin which can be administered intramuscularly. This preparation contains 100 mg. of heparin per c. c., is free from foreign substances or vasoconstrictor agents, and is watery in appearance and viscosity. It has been injected by nurses into the gluteal muscles with the regular intramuscular syringes and needles at eight to twelve hour intervals. The dosage required is roughly correlated with the body weight of the patient. Adequate prolongation of the coagulation time is usually obtained in patients weighing between 100 and 130 pounds by administering 100 mg. every eight hours or 120 mg. every twelve hours. In heavier individuals larger doses may be required. The maximum daily dose should not exceed 450 milligrams. The successful heparinization of patients weighing over 170 pounds may be obtained by giving 1 mg. per pound of body weight as the initial dose and between 0.5 and 0.7 mg. per pound at eight hour intervals subsequently. The medication was administered over a period of several months to most of the postoperative patients of a general surgical service. There was no existing intravascular thrombosis in this group of ninety patients and none developed venous thrombosis. It was found that bleeding at the operative site could be averted if the anticoagulant was withheld until forty-eight to sixty hours had elapsed after the operation. In a small group of cases with thrombophlebitis which the authors have also treated, they observed the same rapid subsidence of fever, tenderness, and edema in the affected extremity that others have described with different preparations of heparin and other anticoagulants.

They conclude that this preparation provides a simple, safe, and essentially painless form in which heparin can be administered intramuscularly to achieve a desired anticoagulant effect.

DURANT.

Parin, V. V.: The Role of Pulmonary Vessels in the Reflex Control of the Blood Circulation. Am. J. M. Sc. 214:167 (Aug.), 1947.

This Russian investigator has studied reflexes originating in the pulmonary circulation in a large series of experiments using cats as the experimental animal. The left pulmonary artery was cannulated and the left pulmonary veins ligated so that, while the left lung had its innervation intact, it was completely isolated from the main blood circulation. Under these circumstances, an increase of pressure in the vessels of the excluded lung caused extensive changes of the whole circulatory system which had incontestably a reflex character. These changes consisted in a reaction which was depressor in type and had two components; a cardiac one with a considerable drop in the heart rate, and a vasomotor one with peripheral vasodilatation. Hence, the reaction was analogous to those observed in the known depressor and carotid reflexes, though not so strong as the latter. This reflex should have an appropriate place among those mechanisms which play an important role in the "automatic" regulation of the circulation. In such increases of pressure in the pulmonary vascular stream as may arise in a number of physiologic and pathologic conditions (Valsalva's experiment, embolism of the pulmonary artery, and so forth), the reflex from the pulmonary arteries, by lowering of the heart action and by transfer of blood into the greater circulation via extensive vasodilatation and increase in the capacity of the depot, prevents the weak musculature of the right ventricle from being overburdened by work. At the same time, this reflex has probably some significance in the prevention of pulmonary edema which easily occurs in cases of prolonged increase of pressure in the pulmonary artery system.

DURANT.

Meneely, G. R., and Segaloff, A.: Observations on the Velocity of the Blood in Normal Men in the Basal State. *Am. J. M. Sc.* 214:176 (Aug.), 1947.

Duplicate determinations of the blood velocity of forty six normal men in the basal state were made with the calcium-magnesium salt mixture of Spier, Wright, and Saylor (Macasol). The arm-to-tongue time was 16.7 ± 4.8 seconds; the arm-to-perineum time, 26 ± 8.4 seconds; the arm-to-hand time, 28.1 ± 6.6 seconds; and the arm-to-foot time, 37.4 ± 9.5 seconds. These times are significantly longer than those previously reported and indicate that measurement of the blood velocity is not as useful as many believe, because the relatively wide range of "normal" values overlaps the "abnormal" values in the very cases wherein the differential significance of the test would be most important. In addition to many previously reported factors affecting the determination of blood velocity, anxiety as a factor could have been a definite variable in one of the experiments. There was no simple relation between the velocity of the blood and the height, weight, age, or pulse rate of the subjects, nor was any seasonal variation perceptible. No untoward reactions of any kind occurred and end points were secured in all but two subjects. One blank occurred, apparently because the subject "pooled" the injected material in the arm; the end point sensation was detected only when he moved his arm to arise after the test.

DURANT.

Robb, J. S., and Turman, W. G.: Further Consideration of the QT Interval. *Am. J. M. Sc.* 214:180 (Aug.), 1947.

A bundle of His is present in the human fetal heart and this tissue merges imperceptibly along a longitudinal axis into heart muscle cells, a given strand supplying a limited area. The possibility exists that this structure, similar in its distribution to the bundle of His and its ramifications in ungulates, is not the "conducting system." If not, and if conduction from auricle to ventricle is by way of nerves, then since no parasympathetic nerves reach the ventricular muscle, the sympathetic nerves would need to be the "conducting tissue." As yet no method has been devised for differential sympathetic staining, and the ultimate distribution of these nerves to ventricular muscle is not known. Hence, if the structure which is similar in distribution to the bundle of His in ungulates is not the conducting pathway, we then know nothing of the conducting system to the ventricle. Because cutting and crushing experiments damage all tissues in this region, such procedures can never determine which tissue serves for conduction.

In accordance with the distribution of this differentially stained tissue and in accordance with much data available in the literature regarding initial negativity of heart surfaces, it is suggested that quite limited areas of heart muscle, "islands," depolarize as a result of stimuli arriving over these numerous anatomic pathways. From studies of the Q-T interval in various species of animals, it is shown that the relationship of this interval to the cycle length is independent of the total mass of the heart. The Q-T duration seems to be directly related to metabolism, presumably cardiac cellular metabolism. In the intact dog, the $\frac{Q-T}{\text{cycle}}$ ratio is decreased by vagal stimulation and increased after atropinization and by accelerator stimulation. Measurements of Q-T made under such conditions that the number of variables active at one time is limited offer an indication of the state of the heart muscle (that is, the effect of increased acetylcholine or epinephrine). Thus Q-T duration for a given cycle length can be varied at will. The reason for lack of "clinical usefulness" of measurements of Q-T may be that the specific effects of all possible variables are not yet known. In laboratory animals the $\frac{Q-T}{\text{cycle}}$ ratio seems more significant than mere Q-T duration.

DURANT.

Logan, M., Ferris, E. B., Engel, G. L., and Evans, J. P.: Arterialization of Internal Jugular Blood during Hyperventilation as an Aid in the Diagnosis of Intracranial Vascular Tumors. *Ann. Int. Med.* 27:220 (Aug.), 1947.

In the course of study of sixty-nine samples of internal jugular blood taken before and during hyperventilation in persons without vascular tumors, it was found that the usual reaction was for

the oxygen content to fall during hyperventilation. In a small percentage of the cases the oxygen content remained unchanged or rose slightly. In a patient with a demonstrated intracerebral vascular tumor in the left frontoparietal region, hyperventilation increased the oxygen saturation of the internal jugular blood to almost arterial levels (95 per cent). This relatively simple procedure is, therefore, suggested by the authors as an aid in the diagnosis of vascular intracranial tumors. It is postulated that the findings reflect a shunting of blood through the vascular anomaly during cerebral vasoconstriction associated with hyperventilation and in this way leads to increased arterialization of the internal jugular blood.

WENDKOS.

Kimball, J. L., and Burch, G.: The Prognosis of the Wolff-Parkinson-White Syndrome. *Ann. Int. Med.* 27:239 (Aug.), 1947.

A 38-year-old woman and a male infant one month old died suddenly during attacks of paroxysmal tachycardia. Electrocardiographic records prior to death indicated the presence of the Wolff-Parkinson-White anomaly in each instance. In the adult, no clinical evidence of associated organic heart disease could be discovered. In the case of the infant, the autopsy did not disclose any evidence of congenital or acquired cardiac defects. On the basis of this experience, the authors suggest that the syndrome of anomalous atrioventricular excitation should not always be considered entirely benign.

WENDKOS.

Katz, L. N., Winton, S. S., and McGibow, R. S.: Psychosomatic Aspects of Cardiac Arrhythmias: A Physiological Dynamic Approach. *Ann. Int. Med.* 27:261 (Aug.), 1947.

The purpose of this paper is to blend together various developments from the fields of psychiatry, physiology, and classical cardiology, with the view of breaking down the provincial barriers of each field in its individualistic approach to the psychosomatic problem of cardiac arrhythmias. It is considered that the summation of the psychic stimuli, regardless of its pattern, must exert its affect through either one or the other division of the autonomic nervous system, as well as the endocrine glands.

The authors accept the view that, since the human heart is under the constant influence of the central nervous system with centers located in the medulla oblongata in the floor of the fourth ventricle, it would be expected that the cardioregulatory centers are influenced by impulses arising from the hypothalamus and cortex. The authors briefly review the experimental studies indicating that cortical stimulation influences the cardioregulatory centers. For instance, stimulation of the anterior hypothalamus produces slowing of the heart rate and prolongs A-V conduction, while stimulation of the posterior hypothalamus causes tachycardia and frequent premature systoles. For this reason, psychic impulses may be expected to upset the tonic balance in the cardioregulatory centers and cause (1) depression or stimulation of the primary pace maker of the heart, producing sinus tachycardia, sinus bradycardia, and sinus standstill; (2) increased irritability of subsidiary pace makers, giving rise to paroxysmal tachycardia of supraventricular or ventricular origin, or to paroxysmal auricular fibrillation and flutter, and even possibly to ventricular fibrillation with sudden death; and (3) heart block, for example, sinoauricular or A-V block and, more rarely, intraventricular block.

The proper management of the psychoneurotic individual suffering from cardiac irregularity is also stressed. Simple principles involving the psychotherapeutic approach are briefly outlined. The point is also made that even though the arrhythmia has been diagnosed as psychosomatic, all aids of examination should be utilized in order to rule out every possibility of an organic basis for the irregularity.

WENDKOS.

McElroy, J. W., Davis, J. P., and Michelson, R. P.: Complete Transposition of the Arterial Trunks with Closed Interventricular Septum. *Ann. Int. Med.* 27:308 (Aug.), 1947.

The authors add one more case to the fifty authenticated cases of transposed arterial trunks with closed interventricular septum reported up to 1929. The patient was an infant who lived for

five weeks, although cyanosis had been present since birth. Death was preceded by the rapid development of respiratory distress and congestive heart failure. Associated anomalies included a patent ductus arteriosus and a patent foramen ovale.

A twin brother in whom a loud basal systolic murmur had been heard at the age of 4 weeks, died at the age of 2 months following a sudden attack of dyspnea and cyanosis. Although some form of congenital heart disease was suspected in this twin infant, autopsy was refused and, therefore, the exact diagnosis was never established.

WENDKOS.

Blakemore, A. H.: The Clinical Behavior of Arteriosclerotic Aneurysm of the Abdominal Aorta: A Rational Surgical Therapy. Ann. Surg. 126:195 (Aug.), 1947.

Blakemore outlines the characteristic features of abdominal aneurysms and differentiates between the arteriosclerotic and syphilitic varieties. The former was encountered twenty-six times, while the latter was observed six times at the Presbyterian Hospital, New York City, in recent years. Arteriosclerotic abdominal aneurysms are fusiform, rarely erode vertebrae (one out of twenty-six cases), originate 3.0 to 4.0 cm. above the orifice of the renal arteries, seldom cause significant symptoms until they leak retroperitoneally, and usually end fatally two to six days after the original rupture. Syphilitic aneurysms of the abdominal aorta, on the other hand, are saccular, usually have their point of origin above the renal arteries, erode vertebral bodies, and therefore, are associated with marked radicular pain.

The author then discusses the hemodynamics of fusiform and wide- and narrow-mouthed saccular aneurysms, pointing out that nature's cure consists in brimful clotting which occurs spontaneously only occasionally in narrow-mouthed saccular aneurysms. The rate of blood flow in the aneurysm is the second important factor in considering a therapeutic approach.

By means of his electrothermic method of coagulating aneurysms, Blakemore can determine the rate of blood flow and hence the type of aneurysm, and further how much wire is necessary to introduce and heat in order to obtain brimful clotting. In fusiform abdominal aneurysms it is necessary to completely occlude the aorta and the aneurysm in stages from within, thereby permitting the development of an adequate collateral circulation to the legs.

The author has dealt successfully with three out of twenty-six cases of fusiform arteriosclerotic aneurysms and two out of six cases of syphilitic fusiform aneurysm of the abdominal aorta.

LORD.

Sanders, J. H., and Isoe, I. M., Intravenous Oxygen and Pulmonary Embolism. Ann. Surg. 126:208 (Aug.), 1947.

The authors studied the arterial oxygen saturations in a group of patients who were subjected to an intravenous injection of oxygen. In the first patient 9.3 cc. of oxygen per minute were administered for twenty minutes and the arterial oxygen saturation fell from 94 per cent to 55.5 per cent. Associated with this fall, the patient experienced a sensation of pressure in the lower chest, cough, restlessness, and profuse perspiration. These symptoms cleared in a few minutes after cessation of the oxygen injection.

Three other experiments in patients not in shock and two in patients in shock further demonstrated that intravenous oxygen is not of value in elevating the arterial oxygen saturation and, on the contrary, actually lowers it. The explanation of this phenomenon is that the oxygen gas bubbles occlude the small arteries and arterioles and are not absorbed by the blood stream. One in vitro experiment demonstrated that a small amount of oxygen bubbled through venous blood does not increase the oxygen saturation.

The authors conclude that intravenous oxygen is of doubtful therapeutic value in the treatment of shock and may actually be harmful.

LORD.

Gross, P., and Benz, E. J.: Pulmonary Embolism by Amniotic Fluid. Surg., Gynec. & Obst. 85:315 (Sept.), 1947.

In addition to the well-known causes of embolism to the lungs, such as thrombi from venous sources in the legs and fat emboli from fracture sites, Gross and Benz report three cases of pulmon-

ary embolism by amniotic fluid. The three cases experienced their emboli near the end of labor or in the immediate puerperium. The event in each case was characterized by shock which rapidly progressed to a fatal termination within one hour of onset. Antishock therapy was without avail.

There are no significant gross pathologic findings. However, the characteristic lesion is seen in the lungs on microscopic examination where there is found in the smaller arteries, arterioles, and alveolar capillaries a bloodless mixture "consisting of abundant polymorphonuclear leucocytes, mucin, bile-stained debris, (meconium), epithelial cells, lanugo hair, and granular debris with or without fatty elements."

The authors point out that examinations and analysis of the centrifuged blood from the right side of the heart reveals three strata in the sediment. "The presence of three instead of two strata should be considered pathognomonic of this condition. The particulate constituents of amniotic fluid including mucus, being of lower specific gravity, settle out as a flocculent layer above the leucocytic cream."

The authors believe that pulmonary embolism by amniotic fluid is a common cause of shock and rapid fatality occurring during labor or in the immediate puerperium.

LORD.

Jones, A. M., and Langley, F. A.: Chronic Dissecting Aneurysm. Brit. Heart J. 8:191 (Oct.), 1946.

The authors report two cases of dissecting aneurysm in which the diagnosis was made during life; one patient survived for three years and the other is alive and comparatively well eight years after radiographic recognition of the aortic lesion.

The first patient had enjoyed good health until the age of 52 years, when she developed a severe stabbing pain in the left anterior chest which radiated to the left scapular region and the dorsolumbar area. After a time the pain abated, and she had no further severe difficulty until the age of 55 years when severe pain in the back of the chest and in the lumbar area forced her to seek hospital care. When admitted to the hospital her blood pressure was 210/135 in the right arm and 195/130 in the left. Fluoroscopy showed gross dilatation of the aorta. The Wassermann reaction was negative. The history and findings led to a diagnosis of chronic dissecting aneurysm. She remained in bed for four months but was never free from pain. Eight weeks after a second admission she collapsed and remained semiconscious until she died four days later.

Necropsy revealed the aorta to be greatly dilated from just below the origin of the left subclavian artery to the level of the diaphragm. At about the middle of the lateral surface of the dilated portion there was a transverse tear 2 cm. long where the aneurysm had ruptured into the left pleural space. On opening the aneurysm two channels were seen. Where the two channels arose from the arch of the aorta the free edge of the septum separating them was rounded and smooth and continuous, with a ridge around the mouth of the larger channel; the free margin had clearly been separated from this ridge when the dissection started and since both ridge and free edge were smooth and healed, this separation obviously was not recent. An unusual feature was the presence of atheromatous plaques on the wall of the aneurysm.

The second patient, a 36-year-old woman, had been well until the age of 30 years, when she began to suffer from severe pain in the back which after treatment with radiant heat and massage had disappeared after several months. A return of these symptoms led to hospital admission. The pulse rate was 120, and the blood pressure, 200/140. The heart sounds were loud but no murmurs were present. Fluoroscopy showed some enlargement of the left ventricle, and considerable diffuse enlargement of the thoracic aorta with calcified plaques in its wall. Kymography revealed quite good pulsations of the descending aorta. An electrocardiogram showed striking left axis deviation associated with diphasic T waves in Leads I and II and depression of the corresponding RS-T segments. She was thought to have a chronic dissecting aneurysm.

While in the hospital she suffered from severe aching pain in the left scapular region, headache, and palpitation. On several occasions she became confused and disoriented. Two years after hospitalization her right arm and leg became paralyzed while she was walking. Some months later she was readmitted to the hospital because of the severity of her epigastric and chest pain. Her blood pressure was then 165/110, and the dorsalis pedis pressure, 205/110. While in the hospital she had two sudden severe attacks of "grinding" pain in the left chest which could be relieved only

by morphia. After her return home the pain continued and became so severe that she returned to the hospital and underwent paravertebral alcohol injection. After this procedure her pain diminished and a year later she was almost entirely free from pain. Two years later fluoroscopy showed some increase in the size of the heart and aorta and calcification of the aortic wall. The right radial pulse was poorer than the left; the blood pressure in the right brachial artery was 200/125; in the left, 215/125; and in the left dorsalis pedis artery, 240/125. At her last examination thirteen years after the onset of symptoms her condition was unchanged.

BELLET.

Nylin, G.: The Effect of Adrenalin Injected Intravenously on the Volume of Circulating Erythrocytes. Acta. cardiol. 1:225 (No. 3 & 4), 1946.

Adrenalin was injected intravenously in eight subjects for the purpose of determining whether any so-called depots empty their blood into the circulatory system. The method used involved the injection of red blood corpuscles labeled with radioactive phosphorus. Small doses of adrenalin caused an increase of systolic blood pressure from 30 to 105 mm. of mercury. The adrenalin action was not followed, however, by any dilution of the circulatory corpuscle volume or by any apparent emptying of blood depots.

LAPLACE.

Charlier, R.: The Circulatory Physio-pathology of Traumatic Arterio-venous Fistulas in Man. Acta. cardiol. 1:232 (No. 3 & 4), 1946.

A study was made of five subjects who had traumatic arteriovenous fistulas. The presence of a traumatic arteriovenous fistula in man induces important changes in the circulatory dynamics. Provided there is no heart failure, these changes include a large increase in the cardiac output per beat and in the minute volume, a rise of right auricular pressure, a fall of arterial pressure, and a slight tachycardia. The tachycardia is induced not only by the arterial hypotension but also by the rise of venous pressure (Bainbridge reflex). From acute experiments performed on dogs anesthetized with chloralose, it appeared that (1) the afferent path of the Bainbridge reflex does not lie exclusively in the vagus nerve, and (2) the tachycardia is induced partly by chemical changes in the blood in the right auricle acting directly or by reflex effect. Mechanical occlusion of an arteriovenous fistula produces a rise of arterial pressure, a fall of venous pressure, a decrease in cardiac output, and a pronounced bradycardia. The bradycardia is not exclusively of vagal origin because slowing of the heart rate still occurs after atropinization. It is due to both a rise of arterial blood pressure and a fall of the central venous pressure (Bainbridge reflex).

LAPLACE.

Bjorck, G., and Pannier, R.: One Hundred Positive Hypoxemia Tests. Acta cardiol. 1:283 (No. 3 & 4), 1946.

The authors studied 100 positive hypoxemia tests which occurred in a series of 666 cases. The technique employed at first involved the inhalation of a mixture of 10 per cent oxygen for twenty minutes. Later, the shorter and more convenient procedure of administering 9 per cent oxygen for ten minutes was used.

It was found that a positive test occurred more often among women than among men. Among patients in whom the test was positive but who showed no clinical evidence of coronary disease, there was a large proportion of cases of hypertension. Most of the latter showed no enlargement of the heart. Among women in whom the test was positive, the nervous and hormonal systems appeared to play an important role.

The authors conclude that a positive hypoxemia test in a patient suspected of having angina pectoris is certain evidence of coronary disease. A positive test can appear in cases of organic coronary disease in the absence of anginal pain. It is apparent that a positive test can occur in patients with functional coronary insufficiency in whom there is no organic coronary disease. Such patients may be said to have a disorder of the vegetative nervous system and require special treatment. The so-called coronary neurosis of purely psychic origin is quite frequent, but in these cases the test is negative.

LAPLACE.

Piron, A.: The Cardiopathy of Friedreich's Disease. *Acta. cardiol.* 1:305 (No. 3 & 4), 1946.

A detailed study of the cardiovascular system was made in two brothers with Friedreich disease. Both patients appeared to have an anginal syndrome and showed electrocardiographic changes consistent with a diagnosis of coronary insufficiency. The author points out that cardiac disorders occurring in the course of Friedreich's disease may reasonably be attributed to the effect of the medullary lesions on the coronary circulation. He concludes that the hypothesis of the medullary origin of angina pectoris is supported by the clinical evidence found in cases of this type.

LAPLACE.

Frimann-Dahl, J.: On Venography of the Lower Extremities. *Acta radiol.* 28:199, 1947.

The author discusses the pertinent information derived from venography in the diagnosis of acute and chronic deep thrombophlebitis of the lower extremities, and advises a number of modifications in the technique in order to avoid certain pitfalls in the interpretation of the films. He calls attention to the finding that if the patient lies in the supine position, with the leg supported on the calf and heel, there will be a defective filling of the deep veins in the muscular pad of the calf with the result that the film may resemble the picture seen in thrombosis of the deep veins in this area. He therefore advocates that all pressure be removed from the calf while the contrast medium is being injected, and also that lateral films should be taken to decide whether an involved vein is superficial or deep.

On the basis of the findings with venography, the author concludes that pressure against the calf veins during rest in bed partly or completely interferes with the return of blood through this system of vessels, and that this mechanism may play an important role in the development of venous thrombosis. Since crossing the legs in bed likewise interferes with filling of the calf veins with the contrast medium, it is possible that this position may also contribute to venous thrombosis.

ABRAMSON.

Long, W. K., and Farah, A.: The Influence of Certain Sulfhydryl Compounds on the Toxicity of an Organic Mercurial Diuretic. *J. Pharmacol. & Exper. Therap.* 88:388 (Dec.), 1946.

Forty deaths following the use of mercurial diuretics have been reported. Experimental study has suggested that the cause of death is due to a toxic action of mercury on the heart, with resultant ventricular fibrillation, or to respiratory failure secondary to a fall in blood pressure. This study evaluates the effect of substances containing the sulfhydryl group on the cardiac toxicity of salyrgan. 2,3 dimercaptopropanol (BAL), cysteine hydrochloride, glutathione, methionine, and cystine were tested.

Three types of experimental conditions were evaluated. Salyrgan was used as the mercurial in each. (1) Mice were given varying amounts of salyrgan and the 50 per cent lethal dose (L.D.50) determined. The sulfhydryl compounds were then injected into mice and followed in one minute by the calculated L.D.50. The protective action of the sulfhydryl compounds was measured by the increasing amount of salyrgan necessary to produce a 50 per cent mortality. (2) Action of salyrgan, protected and unprotected, on the circulation of dogs was determined by simultaneous measurement of blood pressure, venous pressure, heart rate, and electrocardiogram. (3) Action on the heart-lung preparation of Starling was determined by simultaneous measurement of arterial pressure, pulmonary artery pressure, and left and right auricular pressures.

Methionine and cystine were ineffectual in protecting mice against the control L.D.50 of salyrgan. No improvement in circulatory function was noted. BAL, cysteine hydrochloride, and glutathione increased the L.D.50 of salyrgan in mice. Their administration promptly reversed salyrgan-induced heart failure in dogs. The most severe toxic manifestations short of ventricular fibrillation could be reversed. Once ventricular fibrillation had begun, these substances were ineffectual. In the heart-lung preparation, the protective action of BAL, cysteine hydrochloride,

and glutathione was about equal when calculated in terms of sulfhydryl equivalents. In the intact dog, BAL was five to eight times as effective as cysteine hydrochloride and glutathione. None had any effect on spontaneous or sodium pentobarbital-induced cardiac failure in the heart-lung preparation.

GODFREY.

Andre, M. J.: A New Case of a Fatal Attack of Asthma. The Circulatory Manifestations of Asthma. Acta clin. belg. 2:1 (Jan.-Feb.), 1947.

The author reports the case of a 16-year-old girl who died suddenly in the third attack of asthma which had occurred in the space of twelve days. The patient was studied carefully with special reference to the associated disturbance of cardiovascular function.

It is pointed out that the predominant lesion in fatal asthma is acute pulmonary emphysema due to bronchial and bronchiolar block by abnormal glandular secretion. Although death is attributed to anoxia, it is impossible to evaluate the element of circulatory impairment, manifestations of which include cutaneous vasoconstriction, tachycardia, weak pulse, and hypotension. The most characteristic sign is Kussmaul's pulse: weakening or disappearance of the pulse during inspiration. The mechanism of this paradoxical pulse is discussed in detail.

LAPLACE.

Baber, M. D., and Daley, D.: Coarctation of Aorta in Association With Pregnancy. J. Obst. & Gynaec. Brit. Emp. 46:91 (Feb.), 1947.

The literature on the titled subject is reviewed and the description of another case is added. To date, forty-three cases have been reported in which the majority successfully carried through pregnancy. From these reports, it is clear that pregnancy is not contraindicated in the majority of these patients. The authors recommend adequate spacing of pregnancy and the avoidance of late childbearing as a wise precaution. In spite of reassuring results indicating safety of vaginal delivery, the authors have felt inclined "to play safe," and favored delivery by cesarean section of their 26-year-old primipara.

WAGNER.

Dripps, R. D., and Comroe, J. H., Jr.: The Respiratory and Circulatory Response of Normal Man to Inhalation of 7.6 and 10.4 Per Cent CO₂ With a Comparison of the Maximal Ventilation Produced by Severe Muscular Exercise, Inhalation of CO₂ and Maximal Voluntary Hyperventilation. Am. J. Physiol. 149:43 (April), 1947.

In these experiments, the effects produced by breathing high concentrations (7.5 to 10 per cent) of carbon dioxide have been measured in a large number of normal subjects. In addition the maximal respiratory minute volume produced by inhalation of 7.6 and 10.4 per cent carbon dioxide was compared with that resulting from exhausting muscular exercise and maximal voluntary hyperventilation.

When 7.6 per cent carbon dioxide in oxygen was inhaled, the average minute volume of respiration increased to 51.5 liters per minute, pulse rate increased 16.7 beats per minute, and the blood pressure rose 30.8 mm.Hg systolic and 22.2 mm.Hg diastolic. With 10.4 per cent carbon dioxide in oxygen, the respiratory minute volume was 76.3 liters, pulse rate increased 15.6 per minute, and the blood pressure rose 33.4 mm.Hg systolic and 25.0 mm.Hg diastolic. When carbon dioxide inhalation was stopped, diastolic pressure fell abruptly to normal; the respiration and systolic pressure returned slowly to normal.

The symptoms noted with carbon dioxide inhalations were, in the order of frequency, headache, dizziness, and dyspnea. Most of the dizziness was noted in the immediate postinhalation period, the same time as the abrupt fall in diastolic pressure occurred. The observed effect of carbon dioxide, is the sum of a direct carbon dioxide stimulation of medullary centers and a narcotic action which depressed the respiratory center. They conclude that carbon dioxide inhalation in the treatment of individuals with depressed centers (due to anesthesia, morphine, and so forth) may produce further narcosis with or without hyperpnea or hypertension. They recommend a mechanical increase of ventilation if such is desired.

The narcotic effect probably explains the finding that inhalation of high carbon dioxide produces only 43 per cent of maximal ventilation possible by voluntary hyperventilation. Subjects performing muscular exercise do not breathe more than 66 per cent of the maximal capacity, even at a time when their muscles have incurred an oxygen debt. This failure may be due to fatigue of the respiratory muscles or inhibitory factors which are not important in the short (thirty second) maximal breathing capacity test. The abruptness of fall in diastolic pressure suggests a sudden withdrawal of a vasoconstrictor reflex rather than a gradual decrease in stimulant amounts of carbon dioxide acting upon the vasoconstrictor center.

BERNSTEIN.

Quintanilla, R., Krusen, F. H., and Essex, H. E.: Studies on Frost-bite With Special Reference to Treatment and the Effect on Minute Blood Vessels. *Am. J. Physiol.* 149:149 (April), 1947.

The anterior extremities of rabbits were immersed in absolute alcohol to which pieces of carbon dioxide ice were added until the desired temperature was obtained. The extremity was frozen at various temperatures for different lengths of time. Total destruction was obtained in three minutes at -40°C ., and in 20 minutes at $-20^{\circ}\text{Centigrade}$.

The methods of treatment used by the Medical Corps of the Army were found by the authors to give discouraging results. It was impossible to determine by inspection which extremities were frozen beyond hope of recovery and those which were less seriously frozen. This was considered important, because measures which gave good results in mild cases often gave poor results in severe cases. All the recommended methods were useless when applied to severely frozen feet. Untreated control animals obtained the same degree of recovery as did the treated animals. All the methods used were actually no better than no treatment at all. The idea that frostbite resulted in coagulation of the blood in the smaller vessels with eventual anoxia and destruction of the tissue was not confirmed by direct observation of the rabbit ear vessels exposed to the carbon dioxide ice. The vessels were dilated and filled with cells. Their permeability was increased, with the result that plasma escaped and the formed elements were left concentrated in the vessels. An identical picture was seen in vessels of animals whose blood was made noncoagulable by injection of heparin. Prolonged administration of heparin to rabbits whose extremities were frozen did not save the feet or alter the expected course.

BERNSTEIN.

Byer, E. Toth, L. A., and Ashman, R.: Electrocardiographic Changes Induced by Cooling or Warming the Inner Surface of the Dog's Ventricle. *Am. J. Physiol.* 149:264 (April), 1947.

The temperature of the endocardial surface of the dog's ventricle was changed by the introduction into the ventricle, by arterial catheterization, of Ringer's solution at various temperatures. Cooling the inside of the left apex changed the form of and widened the QRS complex and also caused conspicuous increase in the height and width of the T wave. Warming had opposite but less striking effects on the T wave and changed the form of the QRS complex. Ringer's solution at body temperature caused no changes. Cooling the inner surface of the right ventricle caused similar T-wave changes, but reverse effects on the form of the QRS complex. Cooling the basal left endocardial surface caused inversion and widening of the T waves. It is reasonable, the authors presume, to suppose that the electrical effects were, in fact, brought about by a change in rate of repolarization of the endocardial surface as changed by the variable temperature of the endocardial ventricular surface. If justified, it follows that changes in the electrical state of the subendocardial muscle surface play a part in the genesis of the electrocardiogram. They do not claim to directly explain the genesis of the usual upright T wave of the human electrocardiogram, but believe that this experiment is consistent with the view that the upright T wave may be produced mainly by an endocardial-epicardial difference in rate of repolarization.

BERNSTEIN.

DeTakats, G., and Reynolds, J. T.: The Surgical Treatment of Aneurysms of the Abdominal Aorta. Surgery, 21:443 (April), 1947.

The authors review the literature and discuss briefly the six cases of abdominal aneurysm treated successfully by ligation. Successful treatment is defined as survival for more than one year following operation. Three of the six cases had expired two, three and one-half, and one and one-half years after operation. Three others were living at fourteen months, eleven months, and two years after ligation.

DeTakats and Reynolds present six additional cases of arteriosclerotic and syphilitic aneurysms of the abdominal aorta in which an operation was performed. In two of the cases exploration only was carried out because the aneurysms were found to be inoperable. In three cases a one-inch wide, eight-ply layer of cellophane was wrapped around the aorta proximal to the aneurysm and sutured snugly with cotton. The patients lived fourteen months, two years, and eight months after operation. In one case the aneurysm was operated upon and wired on two occasions at a six month interval, but the patient died following a high cordotomy sixteen months later.

The authors point out that the type of cellophane employed for the wrapping of the aorta is important, as certain varieties produce more fibrosis than others. They advocate the implantation of strips of cellophane into subcutaneous pockets to study the reaction of the connective tissue of the patient whose aneurysm is to be treated.

LORD.

Dripps, R. D., and Comroe, J. H., Jr.: The Effect of the Inhalation of High and Low Oxygen Concentrations on Respiration, Pulse Rate, Ballistocardiogram and Arterial Oxygen Saturation (Oximeter) of Normal Individuals. Am. J. Physiol. 149:277 (May), 1947.

Reliable respiratory data are difficult to obtain in normal men because breathing can be regulated voluntarily and is often disturbed by many factors in the environment. In these experiments, subjects were chosen who were familiar with laboratory surroundings and with the experimenters; every effort was made to achieve optimal conditions for obtaining unquestionably reliable data.

An immediate decrease in pulse rate and minute respiratory volume occurred in twenty-eight of thirty-three subjects when inhalation of 100 per cent oxygen followed the inhalation of room air, suggesting that some chemoreceptors of the carotid and aortic bodies are tonically active at the oxygen tension present in arterial blood (90 to 100 mm. Hg). The small degree of this change indicated that they are only minimally active, since an increase in oxygen tension of approximately 570 mm. Hg was followed by only a 3.1 per cent average decrease in respiratory minute volume.

An increased minute volume of respiration was noted in only a few individuals breathing 18 per cent oxygen, the majority showing no significant change until 16 per cent oxygen was inhaled. Individual variability was extreme, and only slight stimulation was noted until 10 or 8 per cent oxygen was inhaled.

Significant increase in pulse rate occurred when the concentration of oxygen in the inspired air was reduced from 20.9 to 18 per cent. Further evidence of the respiratory stimulant action of 100 per cent oxygen and a bradycardia with reduction in cardiac output per minute were obtained.

BERNSTEIN.

White, H. L., Heinbecker, P., and Rolf, D.: Some Endocrine Influences on Renal Function and Cardiac Output. Am. J. Physiol. 149:404 (May), 1947.

The effect of simple hypophysectomy on cardiac output was determined in a series of five dogs. Cardiac output measurements were made by the Fick method on dogs under sodium pentobarbital. Within a few days after hypophysectomy, the cardiac output fell to 50 to 80 per cent of normal, with usually a further fall in about three weeks. There was then no further fall, at least up to four months. The findings indicate that the renal blood flow falls to about the same degree as the cardiac output, and that the fall in oxygen consumption approximately equalled the fall in cardiac output.

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THE IMPORTANCE OF LOCAL HEART ASSOCIATIONS IN THE 1948 CAMPAIGN

Professional cooperation with the American Heart Association's plans for National Heart Week (February 8-14), outlined in the December issue of the Journal, can be exerted most effectively in the organization of local heart associations. Local affiliates of the American Heart Association have been accurately described as "the task forces in the struggle against heart disease." Educational and fund-raising efforts can be most effective in those areas where strong local heart associations are functioning.

Through the local heart association, the individual physician can make a major contribution in assuring support for education, research, and community service, and in making it possible to bring the benefits of scientific research in diseases of the heart and circulation to every citizen.

Despite the tremendous task which still needs to be done at the local level, many states and large communities are without local heart associations. It is hoped that the professional man concerned with cardiovascular ailments will take the leadership in filling this serious deficiency wherever it exists.

Local physicians have formed the nucleus for the creation of American Heart Association affiliates in many communities. The medical and technical guidance they offer is vital in the conduct of field activities and implementation of the national program of the American Heart Association.

In all sections of the United States, physicians have shown an enthusiastic readiness to support the program of the American Heart Association through the very practical method of helping to form local affiliates. In response to many requests for assistance and advice in organizing local associations, the American Heart Association recently published "A Guide to the Formation of Local Affiliates of the American Heart Association." This booklet does not attempt to go into all the detailed phases of local organization and scientific program, but provides a starting point and basic outline for procedure. The guide is available on request.

Among its recommendations, the Guide points out that although medical membership on the local heart association is essential for the exchange of information among physicians and in special scientific activities, the inclusion of a lay group is most desirable for the satisfactory conduct of a real community program which reaches the public. In this, the local structure conforms to the recent reorganization of the American Heart Association which admitted lay members to its governing bodies for the first time.

Lay members of local heart associations should be drawn from among prominent persons associated with business and industry, labor, civic groups, press and radio, advertising and publicity, education and the church. The chief value of the lay members lies in their ability to assist in fund-raising activities, establish contacts and cooperation with other community agencies, and the development of public interest in the local program.

Throughout the planning period, and regularly thereafter, officials of the local association should consult with the American Heart Association whose function it is to guide and integrate the activities of all local associations and serve as a clearing house for their activities.

The twenty-two local heart associations now affiliated with the American Heart Association carry on various types of programs covering a wide range of activities, but, in general, all have

as their common objectives the development of research; the furthering of community programs for the diagnosis, treatment, and prevention of heart disease; and the education of physicians, other professional groups, local agencies, and the lay public.

In organizing a new local association, the problem will arise as to how extensive the initial program should be. The Guide suggests that the first steps in the program may be directed at achieving professional education of physicians, nurses, medical social workers, and teachers, so that they will accept the responsibilities involved in developing a community program; lay education for the guidance of those needing services and the dissemination of information that will urge patients to seek early medical advice; and public relations and fund-raising campaigns designed to publicize and support the program of the local association as well as to provide funds to be distributed on a national basis for research in cardiovascular disease.

The development of a more integrated permanent program will depend upon available funds and facilities.

Additional local heart associations must take their place in the field as rapidly as possible to help implement the 1948 campaign of the American Heart Association in research, education, and community service, for which a budget of \$828,850 has been set. Five hundred thousand dollars of this amount will be earmarked for a research program to include the following elements:

Grants-in-aid to individuals and institutions for basic studies of diseases of the heart and circulation; epidemiological studies of various types of heart disease and rheumatic fever; studies of the relation of social and economic conditions to cardiovascular disease; reevaluation of cardiovascular disability in life, health, and accident insurance; and studies of employment problems of cardiovascular victims.

A \$125,000 educational budget will include postgraduate education of the medical profession through the Scientific Meeting of the American Heart Association; publication of the American Heart Journal and other scientific literature; and preparation of slides, pictures, and exhibits. This section of the budget also provides for health education of other professional groups, including social workers, teachers, school administrators, physical education instructors, school physicians, public health nurses, and public health workers. Health education of the public and publicity for national aspects of cardiovascular diseases round out the educational phases of the budget.

Under the heading of community service, a sum of \$203,850 has been designated for assistance to communities in developing local heart associations and community programs; establishment of standards for the care of patients with cardiovascular disease; stimulation of and aid in establishing rheumatic fever registries; coordination of case findings with the National Tuberculosis Association and other public health agencies; coordination with public health and other agencies in syphilis control; liaison with federal, state and local agencies; coordination of standards and education of employers and trade unions on vocational training, guidance, and placement of persons with cardiovascular diseases; and service as a national information center and clearing house of cardiovascular activities.

Fund-raising plans to support this far-reaching program for 1948 will include continued efforts to secure special gifts and grants for research projects. Physicians can assist in this phase of the campaign by communicating with influential persons in their area, especially those who may be suffering from heart disease, to obtain their financial support.

Physicians are urged to interest laymen in their communities in helping to organize a local National Heart Week campaign. To assist in such efforts, the American Heart Association has prepared a campaign plan book entitled, "Here's How to Fight Heart Disease." The booklet outlines simple steps to be taken in establishing a local Heart Week committee and lists various educational and fund-raising aids (such as the plastic heart collection box) which are available. Copies of the booklet may be obtained by writing to the American Heart Association.

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Proceedings of the Twentieth Annual Scientific Meeting of the American Heart Association June 6 and 7, 1947

This issue of the AMERICAN HEART JOURNAL includes only scientific papers presented at the Twentieth Annual Meeting of the American Heart Association which was held in Atlantic City, N. J., June 6 and 7, 1947.

THE IMMEDIATE ELECTROCARDIOGRAPHIC EFFECTS OF CIRCUMSCRIBED MYOCARDIAL INJURIES: AN EXPERIMENTAL STUDY

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THE electric phenomena associated with the heartbeat have been analyzed with skill and thoroughness by a number of investigators versed in the physical laws which govern them.^{3-9,13,18,20,21} These investigators have done their work so well that the primary task of those whose interest is engaged by these phenomena is no longer the creation of new hypotheses but rather the construction of a rational and consistent system of electrocardiography on the basis of the principles already established. This will require the testing and retesting by experiment and observation of every prediction that these principles suggest, to the end that the limits within which they apply may be defined.

Unless novelty of method affords a fresh approach, any study of the electrocardiographic consequences of myocardial injury is almost certain to be both derivative and repetitive. The methods of the present investigation represent no

Work done in the Department of Internal Medicine, the University of Michigan Medical School, Ann Arbor, Mich., and the Mayo Clinic, Rochester, Minn. The observations reported in this article were made with the aid of a grant from the Kresge Foundation Fund for Research in Cardiology.

Presented at the Twentieth Annual Meeting of the American Heart Association, held in Atlantic City, June 6-7, 1947.

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radical departure from those applied by others. If justification for this report is to be found, it must be sought in more commonplace qualities. It may be that some of the results recounted here define more boldly the structure of the theory to which they afford little needed confirmation; others may establish the conditions which must obtain in order that the results predicated by that theory may evolve; and finally, a report of the initial confusion provoked by certain findings and resolved by more extended investigation may help others to avoid like dilemmas. We are deeply indebted to Dr. Frank N. Wilson and Dr. Franklin D. Johnston for counsel and suggestions in the course of our experiments.

Development of the membrane theory, elaboration of the laws governing the flow of electric currents in volume conductors, and integration of these concepts with the body of electrocardiographic knowledge lie beyond the scope of this report. An extended survey of these and related problems may be found in an earlier paper which, in conception and expression, bears the mark of finality.²⁰ It is pertinent only to review aspects of earlier studies which are related directly to the problem of myocardial currents of injury.

Essential to the production of a current of injury is the existence in the myocardium of a region on one side of which the cell membranes are damaged more severely than on the other. The side of this zone where the injury is most severe may be bounded by a layer of muscle which has been destroyed completely. If dead, this muscle layer has no part in the reactions under consideration and acts only as a portion of the volume conductor surrounding the injured tissue. On the other side of this zone of injury are fibers which may be termed normal in respect to three arbitrarily defined criteria:

1. When the fibers are in the resting phase, a potential difference is maintained across the cell membrane. This potential difference is the product of an orderly orientation of ions disposed in such a way that the external surface of the membrane is positive relative to the internal surface.

2. On the arrival of the excitatory process, a redistribution of ions occurs at the cell membrane attended by a profound alteration of the potential difference between the internal and external aspects of that membrane. This reaction is called depolarization.

3. Following the response to the excitatory impulse with depolarization of the cell membrane, a reorientation of ions occurs with the restitution of the original potential difference across the membrane. This reaction is called repolarization.

Characteristic, then, of fibers lying just outside the zone of injury is the maintenance of a fully polarized membrane during diastole, the occurrence of depolarization on arrival of the excitatory impulse and the restitution of a state of full polarization of the cell membrane following response to the excitatory process.

In what respect does muscle within the zone of injury differ from that which responds to excitation in a manner considered characteristic of the normal myocardium? Two variations may be defined:

1. The voltage across the membrane of the injured fibers may be zero or may reach any fraction of its normal value. The degree of polarization may

vary not only in different portions of the region of injury but also over different portions of the membrane of one and the same fiber. The potential difference across the membrane will, in general, be greatest in the fibers or parts of fibers which have been injured least.

2. On arrival of the excitatory impulse the injured tissue may respond, undergoing the changes of ionic distribution characteristic of this reaction. The possibility exists, however, that some of the fibers in the area of injury do not respond or that only a part of the cell membrane becomes depolarized, the remainder retaining across its surface the potential difference which existed during the resting state.

Muscle within the zone of injury exhibits, therefore, in comparison with that within the "normal" region a reduction, variable in degree, of the voltage across the cell membranes during the resting phase. In addition, some of the injured fibers or portions of fibers may display a state of refractoriness to the excitatory impulse. In a diagrammatic way, the difference between the fibers in the "normal" region and those in the injured region relative to the state of polarization of the cell membrane may be represented as in Fig. 1. In the un-

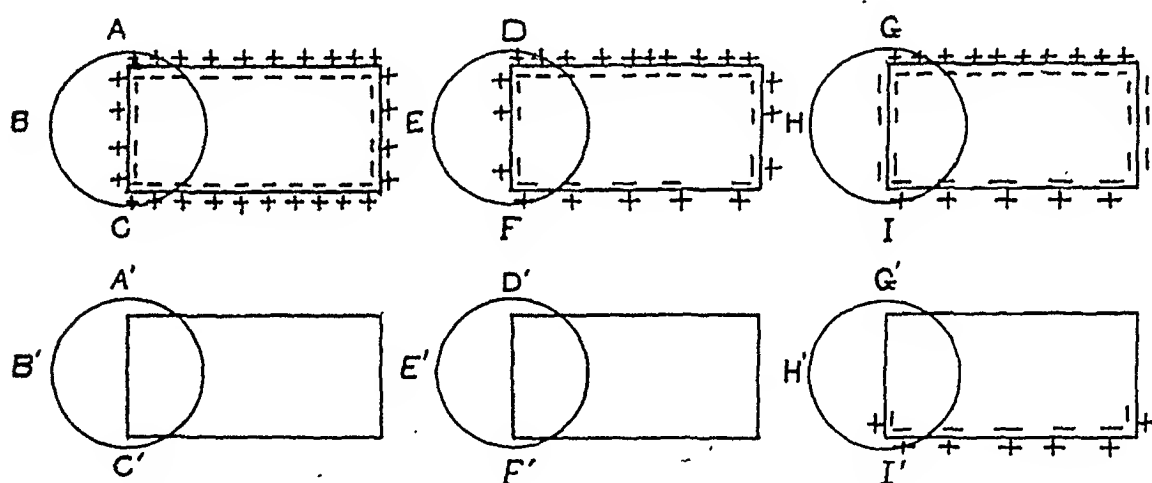


Fig. 1.—Diagrammatic representation of normal and injured cells with respect to the state of polarization existing at the cell membranes during the resting and active stages. For explanation, see text.

injured resting fibers, the voltage across the cell membrane is maximal for cells of this type. The potential difference between the inside and outside of that membrane is the same for all its parts. Hence any possible circuit, ABC , passing through the cell necessarily includes potential drops of which the algebraic sum is zero. This condition which exists in the resting normal fiber obtains also when that fiber has responded to the excitatory process and its membrane is depolarized. Any potential differences maintained at the cell membrane are the same for all its parts and no electromotive force is contributed to any circuit, $A'B'C'$, passing through it.

Only under two circumstances does the normal cell generate an imbalanced electromotive force. It does this as it passes from the resting into the active state, during which time depolarization occurs, and when it passes back from

the active into the resting state during the repolarization process. The normal cell does not contribute to the production of the current of injury.

The source of the current of injury lies within the traumatized tissue. Its existence depends on the first of those two characteristics peculiar to injured fibers. It flows because of variations of voltage across different portions of the cell membranes in the damaged muscle. When traumatized myocardium is included between the terminals of the galvanometer, that part of the current of injury flowing through the instrument is neutralized by a compensating current. Hence, if the current of injury flowed uninterruptedly, its existence would have no effect on the electrocardiogram. The immediate source of the changes in the part of the electrocardiogram inscribed after myocardial excitation is completed must be sought in that second characteristic of traumatized fibers, the peculiarities in their response to the excitatory impulse. If a response occurs in these cells and their membranes are depolarized in greater or lesser degree, then all or part of the current of injury will disappear (Fig. 1, circuits *DEF* and *D'E'F'*). A corresponding fraction of the neutralizing current introduced in the galvanometer will flow unopposed until repolarization occurs. If, on the other hand, certain fibers or parts of fibers in the traumatized muscle are refractory to the excitatory impulse, the situation represented in Fig. 1, circuits *GHI* and *G'H'I'*, may develop. Because the more strongly polarized portion of the cell membrane responds while the remainder does not, an electromotive force will be generated directed in a sense opposite to that of the voltage responsible for the current of injury.

The displacement of the RS-T segment commonly occurring in the presence of acute myocardial injury is a manifestation of the flow of current produced by the electromotive force derived from the refractory portion of the cell membrane combined with some portion of the neutralizing current. The exact importance from the quantitative standpoint of each of these sources of current remains unknown. That monophasic curves can be recorded in the absence of significant myocardial injury has been demonstrated by Ashman and Woody.¹ Deflections of this kind developed when the spread of excitation was blocked at a junction between uncooled and cooled tissue, probably as a result of prolongation of the refractory period in the cooled fibers of the heart muscle. Furthermore, Eyster and associates¹⁰ observed that the displacement of the RS-T segment which occurred at the inception of a myocardial injury exceeded the coincident shift in the diastolic base line of the electrocardiogram. This latter alteration is produced by the current of injury prior to its neutralization by the compensating current and is a measure of its intensity.

These observations afford support to the conclusion that the displacement of the RS-T segment following acute myocardial trauma is not dependent solely on a reduction of the intensity of the current of injury when excitation is complete. It is possible that this displacement is unrelated to alterations of the flow of the current of injury, and is a manifestation only of the imbalance of electromotive forces at the cell membranes within the injured region consequent to variations of their response to the excitatory impulse.

Both the direction and the amount of RS-T displacement produced by an acute myocardial injury depend on the spatial orientation of the injured tissue relative to the electrodes of the galvanometer. If the potential at the indifferent electrode is not influenced significantly by voltages generated within the heart, then the electrocardiogram will afford an uncomplicated record of the changes of potential at the exploring electrode. If the solid angle subtended at the exploring electrode by the bounding surfaces of the damaged muscle includes only portions of those surfaces on which lie the more severely injured cells, the potential at the electrode will be positive during inscription of the RS-T segment. The potential at this period will be negative if the angle subtended at the exploring electrode includes only the less severely injured cells (Fig. 2). If the configuration and orientation of the zone of injury is such that the angle subtended at the exploring electrode by the bounding surfaces of the lesion includes cells of both types, then the potential at the electrode will be the algebraic sum of the electric forces which would be produced by each group of cells in the absence of the other.

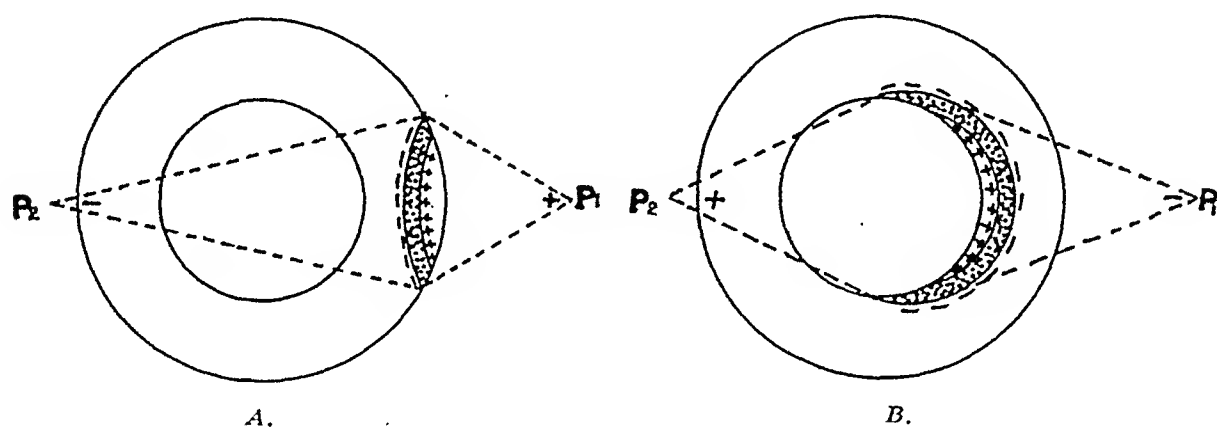


Fig. 2.—A, Diagrammatic representation of the electric field produced at the end of the QRS interval by a region of injured muscle on the epicardial aspect of the ventricular wall. The field is similar to the one which would be produced if the injured muscle (dotted zone) were polarized in the sense indicated. (After Wilson, Hill, and Johnston,¹⁸ 1934.) B represents the field produced by a layer of injured muscle confined to the subendocardial region.

In so brief and dogmatic a statement of the conceptions of the dipole theory as they are related to myocardial injury, accuracy has been sacrificed and ignorance has been veiled. An attempt has been made to arrive at certain points of departure, points which are fundamental in the realm of theory and points which may be tested experimentally.

EPICARDIAL LESIONS

The electrocardiographic phenomena produced by injuring the heart have been investigated carefully.^{6,18,20-22} Wilson and associates¹⁹ in 1934 burned the subepicardial muscle of the ventricle of turtle hearts. Electrocardiograms were recorded with the indifferent electrode placed at a point remote from the heart and with the exploring electrode near or in contact with the ventricular surface. They observed that, apart from a difference of magnitude, the variations of po-

tential at a given point on the ventral surface of the beating heart were similar in all respects whether this surface was exposed to air or was in contact with an external conducting medium. When the muscle beneath the exploring electrode was injured, pronounced displacement of the RS-T segment occurred and the ventricular complex often became monophasic. With connections made so that relative negativity of the exploring electrode produced an upward deflection, the direction of the RS-T displacement was downward. When the subepicardial muscle was injured over a wide area and the injury and the exploring electrode were on opposite sides of the heart, the RS-T displacement was upward and was less pronounced. These investigators analyzed the electric field produced by the injury. It is their conception of this field which forms the basis for Fig. 2, A.

During the course of studies designed to ascertain the effects of lesions involving only the subendocardial layers of muscle, occasion arose to repeat certain procedures of these earlier investigations. In several experiments, observations were made on lesions involving the subepicardial muscle of that portion of the ventral surface which was exposed to air. Electrocardiograms in which relative negativity at the exploring electrode was represented by a downward deflection showed pronounced upward displacement of the RS-T segment when the exploring electrode was on the epicardial aspect of the lesion. However, curves derived from an exploring electrode in the ventricular cavity did not show the distinct downward displacement of the RS-T segment that had been anticipated.

In the experiments of Wilson and associates, the potential inside of the ventricular cavity was not recorded. However, when the subepicardial muscle of the dorsal myocardial wall was burned, relative negativity of the epicardium on the ventral wall was recorded during the RS-T period. If the conductivity of the body tissues is relatively uniform, the electric field corresponding to the forces arising within the injured muscle should be approximately symmetric with respect to the bounding surfaces of that damaged tissue. This being the case, one would expect that in the presence of an acute lesion of the dorsal epicardium, negativity of the ventral epicardium would be attended by negativity of the ventricular cavity (Fig. 2, A).

An obvious discrepancy existed between the preliminary observations of the present investigation and the results predicated on the basis of the conceptions of Wilson and associates. The experiment of the earlier investigation, therefore, was repeated with the intent of recording simultaneously the potential changes in the ventricular cavity and those at the epicardial surface.

Method.—Experiments were performed on turtles (*Graptemys geographica*). The animal was pithed, the heart was exposed by removing the plastron and the preparation was placed with the dorsal side down in a large shallow dish filled with Ringer's solution. A Sanborn Tribeam electrocardiograph was used to obtain two simultaneous records on the same strip of paper. One terminal of each circuit of the instrument was attached to a copper disk 5 cm. in diameter. This electrode was placed in the Ringer's solution at a point as remote as possible from the heart. The other terminal of each circuit was attached to one of the

exploring electrodes. When points on the surface of the heart were to be explored, the electrode consisted of a small glass tube stoppered with salted kaolin and filled with 20 per cent copper sulfate solution into which was thrust a coil of copper wire. Contact with the heart was made by a wick of cotton embedded in the kaolin plug and enclosed in a small rubber tube so that it was insulated to within 1 or 2 mm. of its exposed end. When the potentials within the ventricular cavity were to be recorded, the electrode consisted of a filiform catheter with a core of copper wire. The insulation of the catheter covered all but the tip of the copper wire. The lesions produced in the subepicardial muscle were burns made with a high frequency electrocoagulation unit (Bovie).

Experiment 1.—The turtle was prepared in the usual manner. The filiform electrode was introduced into the ventricular cavity. This was accomplished by making a small incision in the lateral subdivision of the right aorta. The tip of the electrode was slipped into the ventricular cavity and a ligature encircling the artery in which lay the shaft of the electrode was drawn tight. The soft-tipped electrode was placed on the part of the ventral surface exposed to air and simultaneous records were made of the ventricular cavity and epicardial potentials. The epicardial electrode was then removed temporarily. With the electrocoagulation unit, a burn was made on the dorsum of the ventricle. This lesion covered the left half of the basal portion of the dorsal epicardial surface. The soft-tipped electrode was replaced on the epicardium and another set of electrocardiograms was recorded immediately. Subsequent electrocardiograms were made five minutes, twenty-five minutes, and forty minutes after production of the lesion.

The electrocardiograms recorded in Experiment 1 are reproduced in Fig. 3. Downward displacement of the RS-T segment is present in the curves obtained after production of the lesion with the exploring electrode in the ventricular cavity and also in those taken with this electrode on the portion of the ventricular surface which was exposed to air. The amount of displacement is greatest in records obtained immediately after the lesion was produced. Within twenty-five minutes the RS-T segment had returned almost to the isoelectric line in both the epicardial and the cavity leads.

These results are in complete accord with those reported by Wilson and associates and with the conception of the electric field which they advanced. But this confirmation of their observations defined with even greater precision the problem which remained unsolved. Why should the potential within the ventricular cavity be made negative during the inscription of the RS-T segment by an acute lesion affecting the dorsal subepicardial muscle, but remain unchanged when a similar lesion of the ventral subepicardial muscle was produced? The major difference between the two lesions did not appear to be an intrinsic one. In each instance the orientation of the injured and the uninjured muscle relative to the exploring electrode in the ventricular cavity was the same. But a major difference did exist in the environment of the lesion. The injured area on the dorsal surface was completely surrounded by a conducting medium

whereas that on the ventral surface was bounded on one side by air. Determination of the effect of eliminating this difference afforded an attractive approach to the problem under investigation.

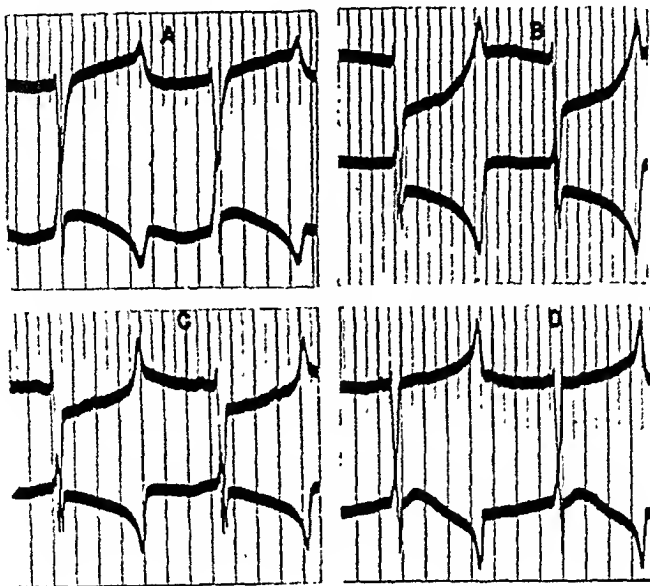


Fig. 3.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the electrode on the portion of the ventricular wall exposed to air. Exact sensitivity is uncertain but it approximates 3 millivolts per centimeter on the ordinate scale. A, Control; B, after burning dorsal surface of the ventricle; C, five minutes after burn; and D, forty minutes after burn.

Experiment 2.—The turtle was prepared in exactly the same manner as in Experiment 1. Electrocardiograms were taken with the exploring electrode of one circuit in the ventricular cavity and that of the other on the portion of the ventral surface exposed to air. A circular pad of cotton, approximately 3 mm. thick and large enough to cover the ventral surface of the heart and extend into the surrounding medium, was soaked in Ringer's solution and laid over the heart. The soft-tipped electrode was placed in contact with the surface of this pad at a site as near as possible to its previous point of contact with the ventricular surface. Another set of electrocardiograms was made. When the pad lay on the heart, the size of the deflections of the ventricular complex was reduced to approximately a fifth the amplitude of the deflections obtained when the exploring electrode rested on the exposed surface of the heart. In order to maintain approximate constancy of the size of the deflections recorded under the two sets of conditions, the sensitivity of the circuit was increased fivefold when curves were taken with the pad covering the heart.

The pad was then removed and with the electrocoagulation unit a burn was made on the exposed portion of the ventral surface of the heart. Thereafter, electrocardiograms were recorded in the same manner and in the same order as the curves taken before the burn. Additional sets of electrocardiograms were made ten minutes, twenty minutes, and fifty minutes later.

The electrocardiograms recorded in Experiment 2 are reproduced in Fig. 4. Examination of these curves reveals that upward displacement of the RS-T

segment is present in those derived from the epicardial electrode after production of the lesion whether the ventral surface was or was not immersed in the conducting medium. On the other hand, downward displacement of the RS-T segment is present in the leads from the electrode in the ventricular cavity only when these were taken while the ventral surface of the heart was covered by the pad soaked in Ringer's solution.

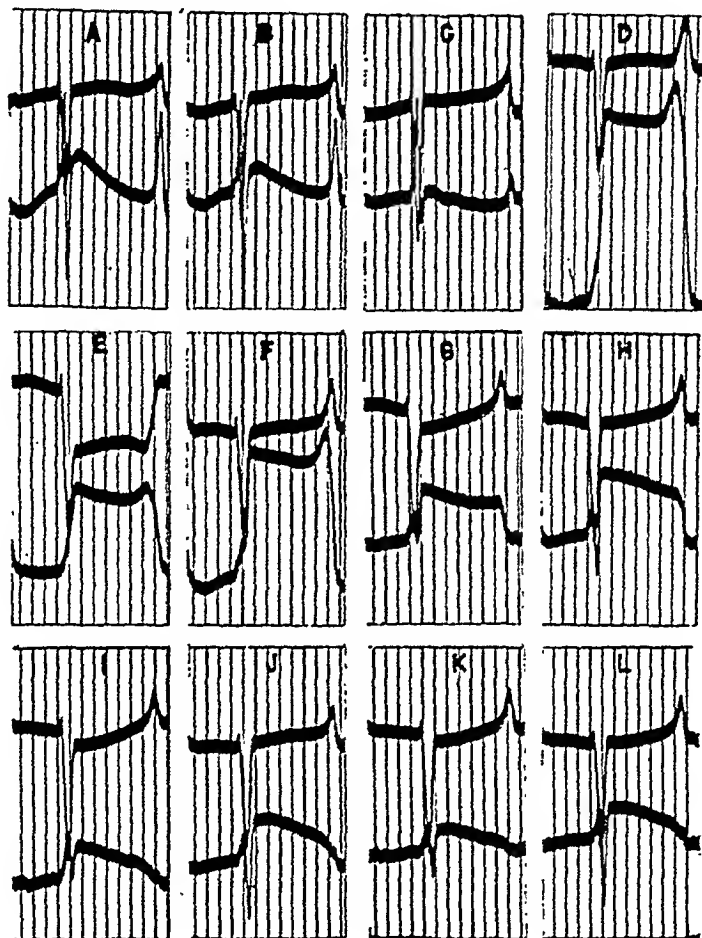


Fig. 4.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the electrode on or adjacent to the epicardial aspect of the ventral wall of the heart. A, Control prior to immersing the dorsal surface of the heart in Ringer's solution; B, control after immersion of the dorsal surface; C, control with ventral surface of the heart covered by a pad soaked in Ringer's solution; D, after burning ventral surface of heart, lesion and ventral wall of heart exposed to air; E, immediately after D, ventral surface of heart covered with a pad soaked in Ringer's solution; F, immediately after E, pad removed from ventral surface of heart; G, ten minutes after burn, pad over heart; H, immediately after G, pad removed from surface of heart; I, twenty minutes after burn, pad over heart; J, immediately after I, pad removed from surface of heart; K, fifty minutes after burn, pad over heart; and L, immediately after K, pad removed from surface of heart.

Ordinate scale: upper curves, 5 millivolts per centimeter; lower curves, 3.5 millivolts per centimeter except when ventral surface of heart was covered by pad, then 0.5 millivolt per centimeter.

It has been observed by others that the distribution of electric forces arising within a region of injury is dependent on environmental factors. Craib⁴ found that the potential at the surface of a partially immersed strip of injured skeletal muscle varied with the position of the injured tissue relative to the conducting medium. Eyster and associates¹⁰ in 1938 commented on the minor changes in the potential of the medium surrounding an isolated quiescent tortoise heart

following injury if the heart were not immersed or if the plane of injury corresponded to that of the field.

It is questionable how much will be gained from an effort to conceive the exact origin and distribution of potential variations within an electric field under the circumstances described in Experiment 2. An analysis will be presented only after according recognition to the fact that it is an explanation designed to fit a limited set of circumstances.

Suppose that a sheet of heart muscle could be isolated in an untraumatized state and then injured in such a way that the cells on one side of the sheet were damaged more severely than those on the other side. A gradient of injury would then exist across the muscle, and current* would flow from the least injured cells on one side to the most injured cells on the other. Within this isolated strip of muscle there must be complete circuits containing the algebraic sum of all the potential drops between the least injured side of the least injured fibers and the most injured side of the most injured fibers. If one electrode were placed on one surface of the sheet and the second electrode on the other surface, the potential difference between the two sides could be measured. Immersion of the muscle in a conducting medium would not be essential to any of these developments.

Suppose the surface of this muscle on which lay only the least injured aspects of the least injured cells was placed in contact with a conducting medium of large extent. All points on this surface would be at the same potential and hence no current would flow between them.

Finally, suppose that both surfaces of the injured muscle were immersed in the conducting medium. Innumerable circuits would now exist, running from the least injured fibers through the conducting medium and back into the muscle sheet on the side where lay the most injured cells.

Thus, if an acutely injured muscle in which a gradient of injury exists is to create an electric field in a conducting medium of large extent, cells lying at different levels on the gradient of injury must make contact with the medium.

Under the circumstances existing when the electrocardiograms reproduced in Fig. 4, *D* were recorded, only the least injured fibers made contact with the medium. Hence, no significant amount of current flowed from the injured tissue into the conducting medium. When one electrode of the galvanometer was connected to the most severely injured cells and the other terminal to the reference electrode in the medium, a circuit was completed and the potential difference across the traumatized tissue was recorded. However, only after the more severely injured fibers were immersed in the medium did any appreciable fraction of the current of injury flow through the ventricular cavity and thence into the circuit of the galvanometer to which the electrode in the cavity was connected.

This analysis appears to afford a reasonably satisfactory explanation for the developments in Experiment 2. It does not lend itself easily to the explanation of even minor alterations in the conditions which existed in that experi-

*In this description, the term "current of injury" is used in the broadest sense. The exact source of the current responsible for RS-T displacement in the electrocardiogram is immaterial to the argument.

ment. In order to arrive at a method more generally applicable, it is necessary to adopt a procedure commonly utilized in computing electric fields in heterogeneous media.¹⁵ This approach, known as the method of images, may be applied in the analysis of problems in which two media are separated by a plane boundary. In Fig. 5, part 1, let the line AB represent a plane surface

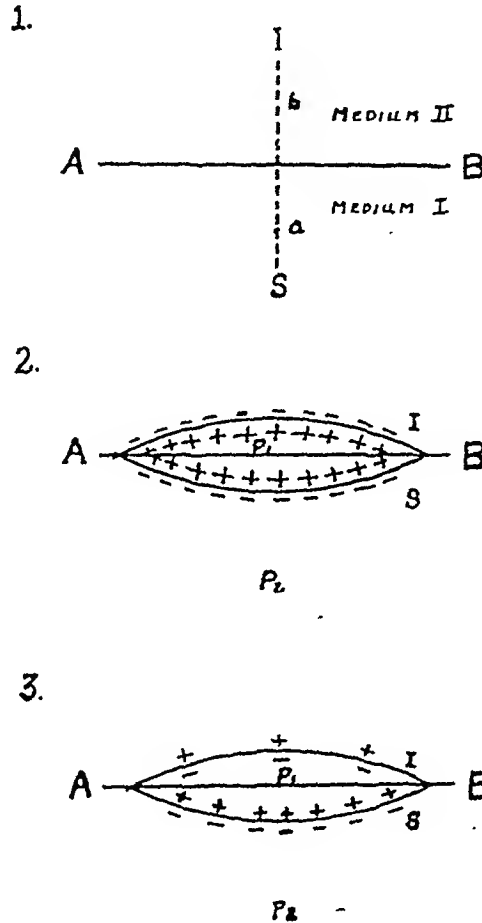


Fig. 5.—The method of images as it applies to the solution of the problem presented by the results of Experiment 2. In all three diagrams, the line AB represents a plane which forms the boundary between two media of different conductivities. S represents a source of electricity in Medium I and I represents its image forces in Medium II. For further discussion, see text.

which constitutes the boundary between two media. Let us suppose that there is a source S of electricity in Medium I at a distance a from the plane surface. Let I in the second medium be the image of S , and let k_1 be the resistance of Medium I and k_2 the resistance of Medium II. It can be demonstrated that the flow of current at any point in the first medium is the same as would be produced by the source S , together with a source $\frac{k_2 - k_1}{k_1 + k_2} S$ placed at I , if the first medium were infinite in all directions. The current at a point in the second medium is the same as would be produced by a source $\frac{2k_2 S}{k_1 + k_2}$ placed at S if the second medium were infinite in all directions.

If the second medium is a perfect insulator, then k_2 is equal to infinity and by the first equation the image at I would be equal to the source at S and of the same sign.

In Experiment 2 the source S in the first medium was represented by the injured layer of muscle, one aspect of which was bounded by a volume conductor of large extent and the other by a nearly perfect insulator, air. The effect of this environmental situation on the distribution of electric forces produced by the lesion may be estimated by applying the method of images. Because the medium on one side of the boundary was a nearly perfect insulator, the images at I and the forces at S would be of the same sign and of equal magnitude. In Fig. 5, part 2, the forces produced by the lesion are represented diagrammatically by a polarized surface S , seen in section. The image forces I are indicated in the same way. It will be seen that the polarized surface S and its image I form a closed space. The positive poles of the elementary voltages are inside this space, the negative poles outside.

At any point P_1 on the epicardial surface of the lesion, the solid angle subtended by the polarized surface S and that subtended by its image I have the same sign and equal magnitude. At any point P_2 which lies outside the injured muscle, the two angles are opposite in sign and equal in magnitude. The potential at any point due to an injured region is roughly proportional to the solid angle which the bounding surfaces of the lesion subtend at that point. It is clear, therefore, that the potential at the epicardial surface of the lesion under consideration would be positive and double what it would be if the medium surrounding the injured muscle were infinite in all directions. The potential at any point outside the zone of injury, on the other hand, would not be influenced significantly by electric forces produced within the damaged muscle.

When the surface of the heart was covered by a pad soaked in Ringer's solution, an environmental situation was created in which the injured layer of muscle was bounded on its epicardial aspect by a medium of higher conductivity than that which lay on the opposite side of the zone of injury. Under such circumstances, by equation 1, the images at I and the forces at S would be of opposite sign and of a magnitude determined by the relative conductivity of the mediums and their extent (Fig. 5, part 3). As a result, the degree of positivity at P_1 would be reduced greatly and significant negativity would develop at P_2 .

An Experiment With Muscle Juice (Experiment 3).—This experiment does not constitute an integral component of the series. It is described because, to us, the results seemed particularly interesting.

The sequence of changes in myocardial injury probably includes (1) an increase of the permeability of the cell membranes; (2) a redistribution of the ions on either side of the cell membranes, and (3) a diminution of the voltage across these membranes, the degree of which is proportional to the severity of the injury.

There is reason to believe that, in these changes which occur after injury, potassium ions are involved. A consideration of the intimate nature of the part which these ions play would extend beyond the authors' knowledge. Two well-

established facts may be cited: (1) The concentration of potassium ions is much higher in intracellular than in extracellular fluids. (2) If a solution containing potassium ions in relatively low concentration (0.1 molar potassium chloride) is applied to the surface of the heart and the exploring electrode is placed on the same area, ventricular complexes of a monophasic type are recorded.

If injuring the cell increases the permeability of its membrane, it undoubtedly leads to diffusion of potassium ions from the intracellular to the extracellular fluid. These potassium ions may be expected to exert on the less severely injured and uninjured muscle an effect similar to that produced by a solution of 0.1 molar potassium chloride. As a minor and perhaps repetitious study of this phenomenon, the following experiment was undertaken.

A turtle was prepared in the manner already described, and control electrocardiograms were taken in the usual way. A small piece of skeletal muscle from the pelvic girdle of the same turtle was chopped into fine pieces and a few drops of juice were squeezed from the macerated tissue onto a piece of dry cotton 8 mm. in diameter. This piece of cotton was laid on the air-exposed portion of the ventricle of the beating heart. The wick of the soft-tipped electrode was placed in contact with the piece of cotton. Two sets of tracings were made. In a second piece of cotton, 3 cm. in diameter, a hole approximately 8 mm. in diameter was cut. This pad was soaked in Ringer's solution and placed on the surface of the heart in such a way that the borders of the hole made con-

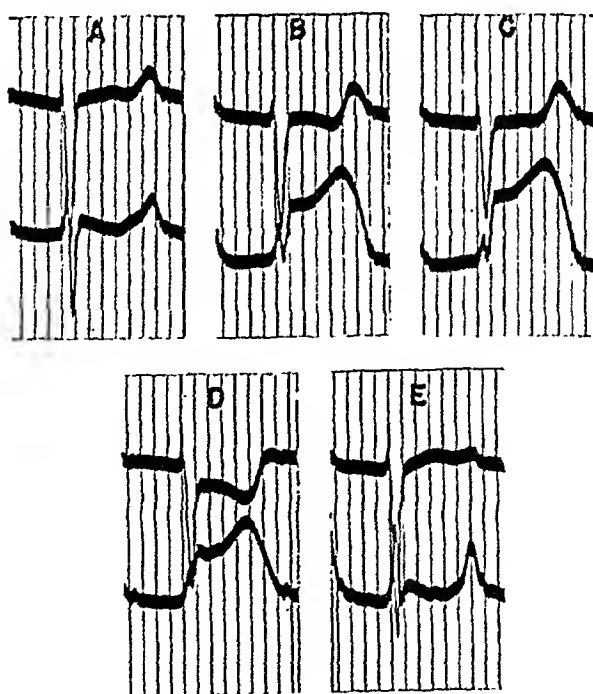


Fig. 6.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves, with the exploring electrode on or adjacent to the ventral aspect of the heart wall. A, Control; epicardial electrode resting on surface of heart; B, after placing small pad soaked in muscle juice between the epicardial electrode and the ventral surface of the heart; C, one minute after B, conditions unchanged; D, two minutes after B, air-exposed portion of ventral surface covered by a cotton pad soaked in Ringer's solution; and E, after both pads had been removed and surface had been rinsed repeatedly with Ringer's solution.

Ordinate scale: upper curves, 5 millivolts per centimeter; lower curves, 3.5 millivolts per centimeter except in D, where a scale of 0.8 millivolt per centimeter existed.

tact with the margins of the pad soaked in cellular juice. Another set of electrocardiograms was recorded. Both cotton pads were removed and the surface of the heart was rinsed repeatedly with Ringer's solution. A final set of electrocardiograms was recorded.

The electrocardiograms recorded in Experiment 3 are reproduced in Fig. 6. In the curves derived from the electrode placed in contact with the small cotton pledget soaked in muscle juice, upward displacement of the RS-T segment was always present. Downward displacement of the segment occurred in leads from the electrode in the ventricular cavity only when the exposed surface of the heart was covered with a larger pad soaked in Ringer's solution. These findings are similar to those obtained when the subepicardial muscle at a comparable site was burned.

The results of this experiment indicate that in the fluid which can be squeezed from severely damaged muscle cells of a turtle there is a substance which, when applied to the beating heart of the same animal, will produce changes in its action currents like those which follow injury inflicted on the myocardial cells by mechanical or thermal means.

ENDOCARDIAL AND SUBENDOCARDIAL LESIONS

Large myocardial infarcts which involve only the subendocardial muscle occur very rarely in man and lesions of this kind are difficult to produce in animals. Hence, the electrocardiographic changes related to acute injuries in the subendocardial region have remained problematic. It seems to be generally agreed that such lesions produce depression of the RS-T segment in the standard limb leads and often in the precordial leads as well. Wolferth and associates²² recently have proposed certain generalizations in explanation of this phenomenon. They divided RS-T displacements into primary and secondary types, defined as follows: displacement of the primary type results from physicochemical disturbances in the fibers directly beneath the exploring electrode; displacement of the secondary type is recorded over the surface of uninjured muscle as a result of changes of potential produced at that surface by forces generated in injured muscle elsewhere in the heart. In the language of Lewis and Rothschild, the first is intrinsic and the second extrinsic in origin. In the experimental results reported by Wolferth and associates,²² primary RS-T displacement, with one possible exception, was always positive and secondary displacement always negative. Since endocardial lesions consistently bear a secondary or extrinsic relation to an electrode placed on the epicardial surface of the heart, the resulting displacement of the RS-T segment is downward.

Between the predictions based on these generalizations and those derived from the concepts of the dipole theory outlined, there is seldom a significant difference. However, on the basis of the dipole theory, an endocardial lesion may produce upward displacement of the RS-T segment in a lead from an electrode placed on an uninjured epicardial surface. This possibility is illustrated in Fig. 2, B, in which a subendocardial lesion is represented. An electrode placed at P_1 lies in a portion of the cardiac field which should be at a negative potential

at the end of the QRS interval. Under the circumstances postulated, an electrode placed at P_2 on the epicardial wall opposite the lesion would lie in the positive portion of the field and in a lead from this point the RS-T segment would be displaced upward.

Consideration of these relationships identifies one requirement which should be satisfied in an investigation of the electrocardiographic changes produced by acute subendocardial injuries. Curves should be recorded not only from points on the epicardium overlying the injured muscle but also from the epicardial surface of uninvolved parts of the ventricular walls.

The difficulties encountered in attempts to produce endocardial lesions justify extended consideration of other aspects of this problem. If the effects of damage to the endocardial and subendocardial tissue on the potential at an electrode outside the heart are to be ascertained, then the lesion must be satisfactory in certain respects.

1. It should be large enough and severe enough to generate an electric field of measureable intensity in the conducting medium surrounding the heart.

2. The boundaries of the lesion should meet the following specifications: first, the zone of damage should be thin, so that a layer of uninjured cells lies between the traumatized tissue and the epicardium; and second, the injured cells should be oriented in such a way that all the electric forces produced by them have a similar effect on the potential of an electrode placed on one side of the lesion.

The production of a lesion which meets these requirements is not accomplished easily nor frequently. The very architecture of the heart renders difficult their fulfillment. The epicardium presents a relatively broad smooth surface readily accessible to traumatizing procedures. The area of the endocardial surface is much smaller, its configuration is irregular and its approach is difficult. If a lesion is to be large and still meet the demand that all its parts contribute forces of like sign to the electric field, then it must involve most of the endocardial aspect of either the ventral or the dorsal wall of the ventricle without extending into the endocardial tissues on the opposite side of the ventricular cavity. Experience soon reveals that in the production of so large a lesion on one wall, injury to the other wall is likely to occur, particularly near the apex.

Limitation of the thickness of the traumatized zone can be achieved more satisfactorily by the electrocoagulation technique than by any other method which we have devised. Yet an unusually prolonged or intense flow of the traumatizing current may result in extension of the injury to the epicardial tissues.

The two experiments described here were selected from a series of thirty-five. In these two instances among all the experiments the electrocardiographic changes were greatest, but in them also the criteria defined in the preceding paragraphs were most nearly fulfilled.

Method.—Turtles were used. The earlier experiments were undertaken on small specimens (*Graptemys geographica*) measuring 6 to 8 inches (15 to 20 cm.) in diameter. In such animals the heart is small and the production of a well-localized subendocardial lesion was found to be exceedingly difficult. Large

snapping turtles (*Chelydra serpentina*) were then secured. Each of these animals measured 12 to 14 inches (30 to 36 cm.) in diameter and weighed approximately 10 pounds (4.5 kilograms). Following an initial series of experiments on twenty small turtles, a second series was carried out on fifteen of the larger animals. An endocardial lesion of some type was produced in all except two of these turtles.

The myocardium was injured by electrocoagulation. The method was identical with that employed in damaging the subepicardial tissues. In the experiments on small turtles, the filiform electrode previously described was introduced into the ventricular cavity by way of the lateral branch of the right aorta. This electrode was used both for recording potentials in the ventricular cavity and for applying the electrocoagulating current. In the experiments on the larger turtles, an enameled copper wire 1.2 mm. thick with a rounded tip was substituted for the filiform electrode.

The large turtles were not placed in a dish filled with Ringer's solution. In the experiments performed on them, the indifferent electrode was a copper disk, 2 cm. in diameter, placed on the subcutaneous tissues of the left hind leg.

Experiment 4.—This was an experiment on a small turtle. The animal was prepared in the usual manner. Two leads were taken simultaneously; one recorded the potential of the ventricular cavity, and the other, the potential at a point on the central portion of the exposed ventricular surface. With the filiform electrode attached to the electrocoagulation unit, an endocardial burn was made. Electrocardiograms were made in rapid succession under conditions noted in the legend of Fig. 7.

Post-mortem examination of the heart revealed a lesion involving the entire endocardial aspect of that portion of the ventral wall lying to the left of the band of muscle which represents the primordial septum. The apparent thickness of this lesion was 1 mm. or less.

Electrocardiograms recorded in Experiment 4 are reproduced in Fig. 7. The results of this experiment are presented for two reasons. The first of these is that the curves obtained exhibit displacement of the RS-T segment induced by extensive injury of subendocardial tissues of the ventral wall of the heart. The contrast between the electric field on one side and that on the opposite side of the injured region is illustrated. The RS-T displacement in the leads from the epicardial electrode is downward, whereas, in those from the cavity electrode, the RS-T displacement is upward. These findings are consistent with the postulates of the dipole theory.

The second reason for presenting these data is that they illustrate a problem which arose frequently in this series of experiments; namely, the effect on the form of the electrocardiogram of changes in the electrical properties of the immediate environment of the heart. In Experiment 2, an example of this effect as it occurs in epicardial lesions was presented and discussed at length. Review of the electrocardiograms reproduced in Fig. 7 indicated to the observers that in the presence of endocardial injury an abundance of free fluid on the surface of the heart has an effect similar to that produced by covering the air-exposed

portion of the surface with a thin cotton pad soaked in Ringer's solution. Either of these environmental factors could be effective in one or both of two ways: either by altering the distribution of cardiac currents or by changing the nature of the contact between the soft-tipped electrode and the ventricular surface. When all free fluid is removed from the air-exposed portion of the ventral surface of the heart and from the cotton wick at the tip of the exploring electrode, the area of contact between the epicardial surface and the wick is small and is subject to variations during different portions of the cardiac cycle. A relatively constant contact can be effected only by pressing the wick of the electrode firmly

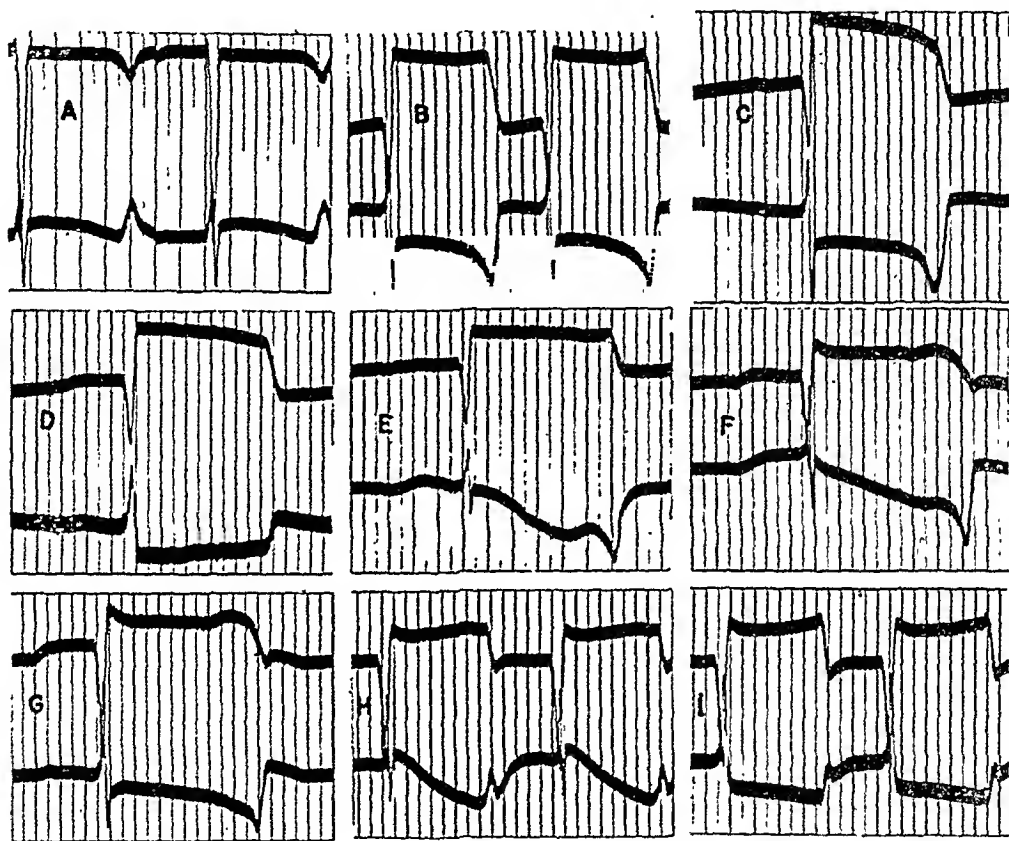


Fig. 7.—Upper curves were recorded with the exploring electrode in the ventricular cavity; lower curves with the exploring electrode on or adjacent to the epicardial aspect of the ventral wall of the heart. A, Control; B, after making a burn on the endocardial aspect of the ventral wall of the heart, ventral surface of heart partially immersed in Ringer's solution; C, immediately after B, 2:1 auriculo-ventricular block had developed and persisted until curves reproduced in H were recorded; D, air-exposed portion of ventral surface of heart covered by a pad soaked in Ringer's solution; E, after removing all fluid from ventral surface of heart; F, five minutes after burn, no free fluid on ventral surface of heart; G, immediately after F, pad covering heart; H, ten minutes after burn, all free fluid removed; and I, immediately after H, pad covering ventral surface of heart.

Sensitivity of galvanometer circuit was increased approximately fivefold in recording curves from epicardial electrode when pad soaked in Ringer's solution covered ventral surface of heart.

against the epicardium. However, this procedure may itself injure the subepicardial muscle and produce changes in the form of the electrocardiogram. Covering the heart with a pad soaked in Ringer's solution or immersing it in free fluid permits the establishment of a constant contact between the heart and the exploring electrode.

It is difficult to ascertain whether the changes in the electrocardiogram which attended immersion of the heart in Experiment 4 were related primarily to alterations of the electric field produced by the injured muscle or to the establishment of a better contact between the electrode wick and the cardiac surface. These changes were not striking in leads from the electrode within the ventricular cavity. In such curves the upward RS-T displacement was slightly greater when a pad covered the heart than it was when the ventricular surface was exposed to air (Fig. 7, *H* and *I*). With the same variation in the environmental circumstances a greater change occurred in leads from an electrode placed at a point outside the heart. When the ventral surface of the heart was bounded by air, the junction of the S wave and the S-T segment was above the isoelectric line in an epicardial lead from the exposed region. In a similar lead taken with a pad covering the heart, this junction was on a level below the isoelectric line near the point occupied by the spike of the S wave in the preceding curves.

It appears probable that most of these changes in the ventricular complexes of leads from the epicardium were due to variation in the contact made by the electrode with the heart. The conclusion is not justified, however, that all of them certainly were related to this factor. If an alteration of the electric field produced by the lesion did occur, the origin of the change may have been similar to that postulated in the discussion of a similar situation which obtained in Experiment 2.

Experiment 5.—This experiment was performed on a large turtle. The animal was prepared in the usual manner. In order to obtain electrocardiograms from the dorsal epicardial surface, a piece of enameled copper wire was used. The distal end of the wire was rolled into a coil 8 mm. in diameter, from one side of which the enamel was removed. The surface of the coil was flat and smooth. The coil was placed in the pericardial sac, resting lightly against the epicardium of the dorsal ventricular wall near the base of the heart. The shaft of this electrode was sutured firmly to the adjacent tissues. Electrocardiograms were taken by leading from electrodes placed on the dorsal and ventral epicardial surfaces and from an electrode in the ventricular cavity. A second set of curves was recorded after the ventral surface of the heart was covered with the pad soaked in Ringer's solution. A lesion was produced with the electrocoagulation unit. Thereafter, electrocardiograms were recorded in the manner and at the times designated in the legend of Fig. 8. Post-mortem examination revealed that the lesion involved the endocardial aspect of the entire ventral wall of the ventricle. Even the ridge of muscle which represents the primordial septum was burned. The apparent depth of the lesion was 1 mm.

The electrocardiograms recorded in Experiment 5 are reproduced in Fig. 8. After the subendocardial injury was produced, the changes in the QRS complexes of the leads from the dorsal and those of the leads from the ventral surface were opposite in character. Prior to the production of the injury, the QRS deflections had essentially the same form in leads of both kinds. A broad R wave was followed by an S wave of approximately equal amplitude. After the

injury, the complexes of the leads from the ventral epicardium consisted of a small Q wave followed by a broad R wave. The S wave had disappeared. The complexes recorded from the dorsal epicardial surface also underwent alterations in form. The R wave became narrower and the S wave broader and deeper.

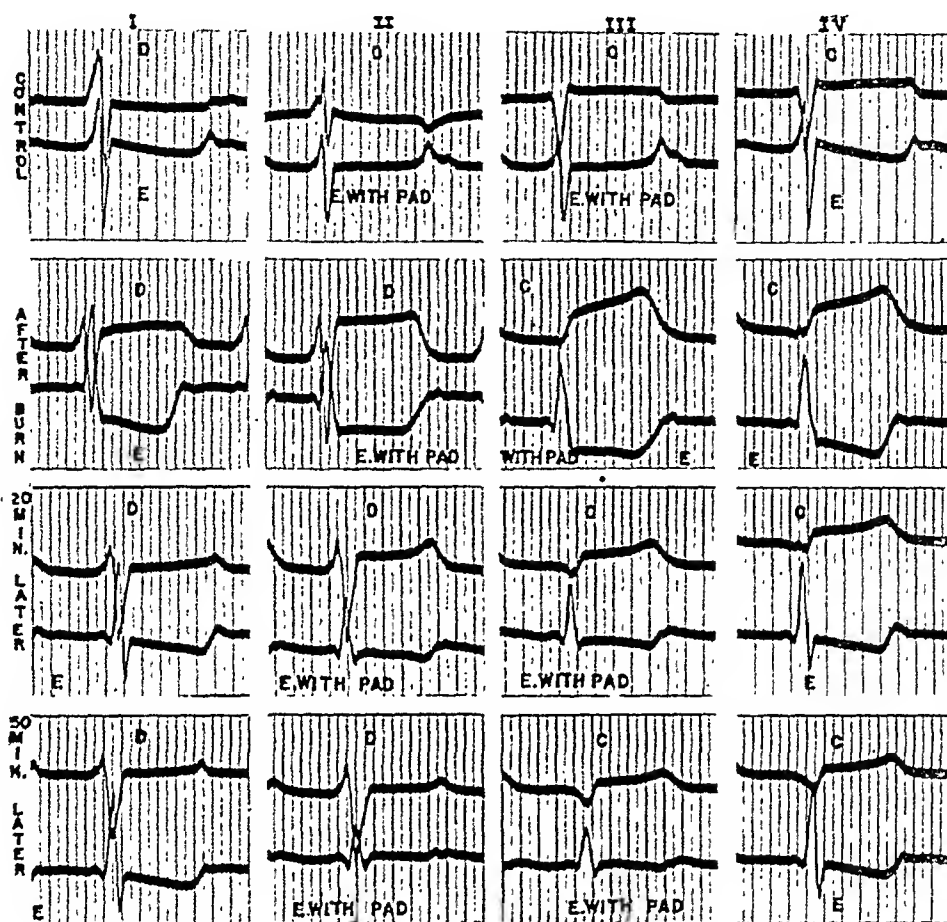


Fig. 8.—Upper curves in Columns I and II were recorded with the exploring electrode on or adjacent to the epicardial aspect of the dorsal ventricular wall (*D*); upper curves in Columns III and IV were recorded with the exploring electrode in the ventricular cavity (*C*). The lower curves were recorded with the exploring electrode on or adjacent to the epicardial aspect of the ventral wall of the heart (*E*). In Columns I and IV, the ventral surface of the heart was exposed to the air; in Columns II and III the ventral surface was covered with a pad soaked in Ringer's solution. Records were made at times indicated along left hand margin of figure.

Ordinate scale: in curves derived from ventricular cavity, 5 millivolts per centimeter; in curves derived from dorsal surface and from exposed ventral surface, 3 millivolts per centimeter; in curves derived from surface of pad covering ventral wall of heart, 0.5 millivolt per centimeter.

These electrocardiograms suggest delayed activation of the ventral wall of the heart. Changes in the QRS complexes similar in character and magnitude to those recorded in this instance were not encountered in any other experiment of this series. Their occurrence may have been due to the large extent of the endocardial lesion or to the involvement of some portion of the heart wall essential to rapid propagation of the wave of excitation.

The RS-T displacements recorded in Experiment 5 are readily perceptible. Subsequent to the production of the endocardial lesion, upward displacement was present in leads from the ventricular cavity and in leads from the dorsal

epicardium. When the exploring electrode was on the ventral epicardium and, therefore, on the opposite side of the injured layer, the displacement was downward.

These results afford evidence that the direction of the RS-T displacement produced by injury to the endocardial and subendocardial tissues depends primarily on the orientation of the lesion relative to the exploring electrode. The presence of uninjured muscle between the electrode and the lesion is significant in determining the direction of the displacement only when the uninjured myocardium underlying the exploring electrode constitutes one boundary of the injured region. In this case the electrode lies on that side of the lesion where the injury to the muscle is least. From an electrode so located, downward displacement of the RS-T segment will be an invariable derivative.

The results of Experiment 5 suggest also that upward displacement of the RS-T segment may be recorded in the absence of significant injury to the muscle cells underlying the electrode. For the appearance of upward RS-T displacement, it is necessary and sufficient that the exploring electrode face the side of the lesion on which the injury was most severe. In lesions produced by traumatizing the subepicardial layers, the region of most intense injury is also the most superficial. From an electrode placed on the surface of such a lesion, curves will be derived in which the RS-T displacement is upward. But when a lesion is produced by traumatizing the endocardial and subendocardial layers of muscle, the most severely injured cells are on that aspect of the lesion which faces the ventricular cavity. An electrode placed on the epicardial aspect of the opposite ventricular wall may lie within the electric field of that lesion at a point where the potential at the end of the QRS interval is positive enough to produce significant upward displacement of the RS-T segment.

If, in the electrocardiograms commonly recorded, subendocardial injury is attended more frequently by depression than by elevation of the RS-T segment, the explanation must be sought in the orientation of the injured muscle relative to the leads used. Such an explanation may be derived from concepts compatible with the dipole theory.

In an earlier investigation by one of us, in association with Barnes and Essex,¹⁷ changes in the electrocardiogram induced by injuries confined to the endocardial and subendocardial tissues were recorded in a series of experiments on dogs. Extensive lesions were produced by mechanical means. The leads used were from an exploring electrode on the thoracic wall at a point overlying the injured region to an indifferent electrode on the right foreleg. Displacement of the RS-T segment was neither a consistent nor an impressive feature of the records obtained. The explanation of its absence remained obscure. In the present series of experiments, the production in dogs of lesions restricted to the endocardial tissues was not undertaken. We feel, however, that a brief discussion of this unsolved problem of the earlier investigation and its relation to the findings just reviewed is desirable.

The electric manifestations of cellular injury appear to be similar in turtles and dogs. In contrast, the spread of the wave of excitation is significantly different in the two species. In the heart of the turtle, no system of tissue special-

ized for the conduction of this wave has been identified. Its spread occurs ordinarily in the direction of a line pointing from the left basal to the right apical region of the ventricle.^{11,13,16} Epicardial points are activated later than the endocardial points immediately underlying them. In the canine heart, a ventricular system for conducting the excitatory impulse is well developed. The entire endocardial aspect of the ventricular walls probably is activated almost simultaneously. The major portion of the QRS complex is formed while the wave of excitation is spreading across the wall from within outward. However, it appears unlikely that the course taken by this wave could influence portions of the electrocardiogram written after the impulse has completed its spread to all parts of the ventricular muscle. If valid, this principle would apply whether the heart under consideration was that of a dog or that of a turtle. Therefore, the effects of endocardial and subendocardial injury on the level of the RS-T junction and segment should not depend on the mode of propagation of the wave of excitation.

In all probability, the failure in the earlier experiments on dogs to record results similar to those subsequently obtained in turtles was dependent on some factor or factors other than the course pursued by the excitatory impulse. Two of these factors may be mentioned.

In the experiments on dogs, no effort was made to produce lesions so located that all of the resulting electric forces would have essentially the same orientation. In many of these experiments, the area of injury extended over the subendocardial muscle of the entire apical portion of the left ventricle including the septum. Under these circumstances the potential changes at a point on the thoracic wall overlying the lesion would represent the algebraic sum of electric forces of one kind from the injured region on one wall of the left ventricle and forces of inverse polarity from the injured region on the opposite wall. Because the traumatized muscle on the ventral side was nearer the exploring electrode than that on the dorsal side of the heart, the electric forces derived from the former perhaps should have been somewhat stronger than those derived from the latter. Without more detailed knowledge than is available, however, it is difficult to estimate what the net effect of combining the opposing forces might be.

It may also be pointed out that the lesions produced in the earlier experiments were not only large; they were also deep. In some places they extended through as much as a third of the thickness of the left ventricular wall. In the following section, the possible consequences of this circumstance on electrocardiograms derived by direct or indirect leads will be considered.

TRANSMURAL LESIONS

Early in the course of our experiments an attempt was made to conceive the sequence of electrocardiographic changes which would occur as a lesion was extended from the endocardium through the ventricular wall toward an electrode on the opposite epicardial surface. The diagram in Fig. 9 represents the concept reached. If the lesion initially involved only region *a*, and then was extended gradually to the size of region *c*, the negativity at the exploring electrode should

increase as the boundary of the injured zone advanced toward the surface. If, in the acute stage of lesion *c*, another lesion was produced on the epicardial side at *d*, the resulting positivity at the electrode due to the second lesion should cancel the negativity due to the first. The amount of RS-T displacement under these final circumstances should be slight. An attempt was made to perform an experiment in which such an extending lesion was created.

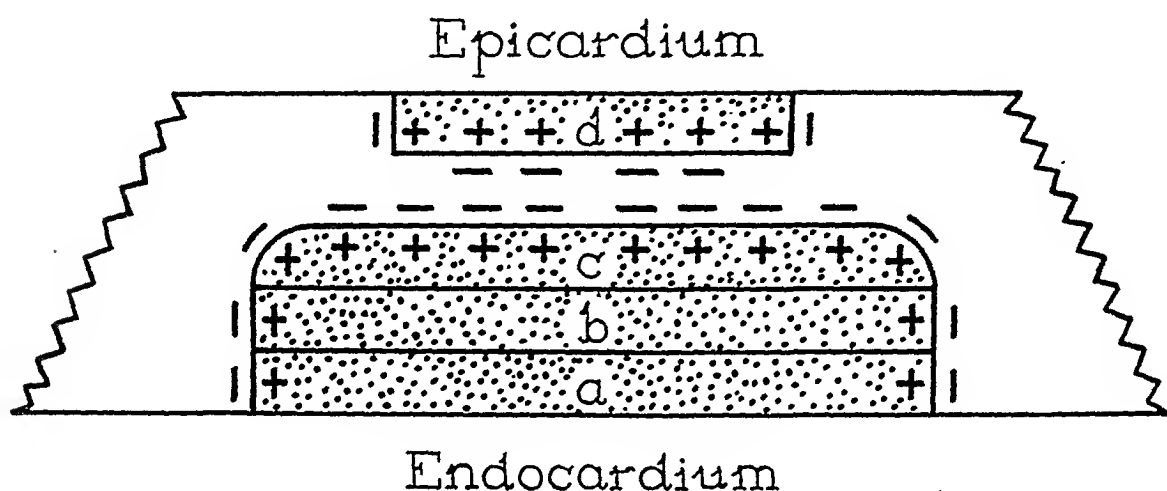


Fig. 9.—Diagrammatic representation of a lesion extending in stages *a*, *b*, and *c* from the endocardial toward the epicardial aspect of the heart wall; *d*, represents an injury to tissue at the epicardial aspect of the wall. For discussion, see text.

Experiment 6.—A small turtle was prepared in the usual manner. The filiform electrode was introduced into the left ventricular cavity. Electrocardiograms were recorded from the soft-tipped electrode resting on the epicardium of the ventral wall of the heart both before and after introduction of the filiform electrode into the ventricular cavity. Through the filiform electrode the electrocoagulating current was applied to the endocardial aspect of the ventral wall. The strength of the current and the duration of its flow were increased step by step. An electrocardiogram was recorded after each application of the current.

The soft-tipped electrode was then removed from the epicardial wall. With another electrode, a burn was made on the surface of the ventricle. This lesion overlaid but was smaller than the endocardial burn. The soft-tipped electrode was returned to its original position and a final electrocardiogram was recorded.

Post-mortem examination revealed that the endocardial burn was 7 mm. and the epicardial burn 4 mm. in diameter.

The electrocardiograms recorded in Experiment 6 are reproduced in Fig. 10. Only in those recorded immediately after the initial endocardial injury does the sequence of changes follow the anticipated course. Slight downward displacement of the RS-T segment is present in the curve labeled *C* in Fig. 10. In subsequent records, upward displacement of the RS-T segment is present and steadily increases. In those taken after the production of the epicardial lesion,

the RS-T segment does not become isoelectric but rises still higher to form curves of a monophasic type.

For this discrepancy between the predicted and the recorded results, there is a simple, if initially elusive, explanation. A zone of injured muscle across which a gradient of injury exists and from which a current of injury is derived

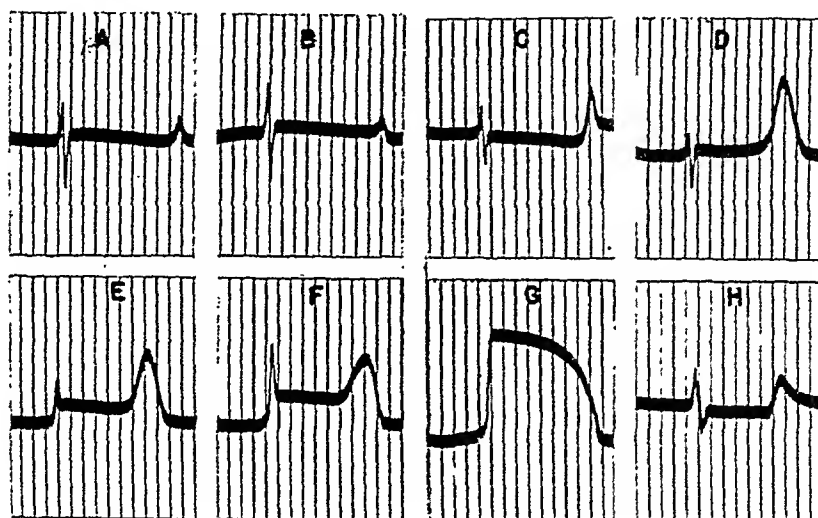


Fig. 10.—All curves except *H* were recorded with the electrode at the same point on the exposed portion of the ventral wall of the heart. *A*, Control; *B*, control after tip of electrode of the electrocoagulation unit had been introduced into the ventricular cavity; *C*, after making initial burn on endocardial aspect of ventral wall of heart at a point underlying the epicardial electrode; *D*, after second burn; *E*, after third burn; *F*, after fourth burn; *G*, after making small burn on the epicardial surface at a point overlying the endocardial burn; and *H*, epicardial electrode shifted onto uninjured muscle at right side of ventral wall of heart.

Ordinate scale uncertain, but approximately 3 millivolts per centimeter.

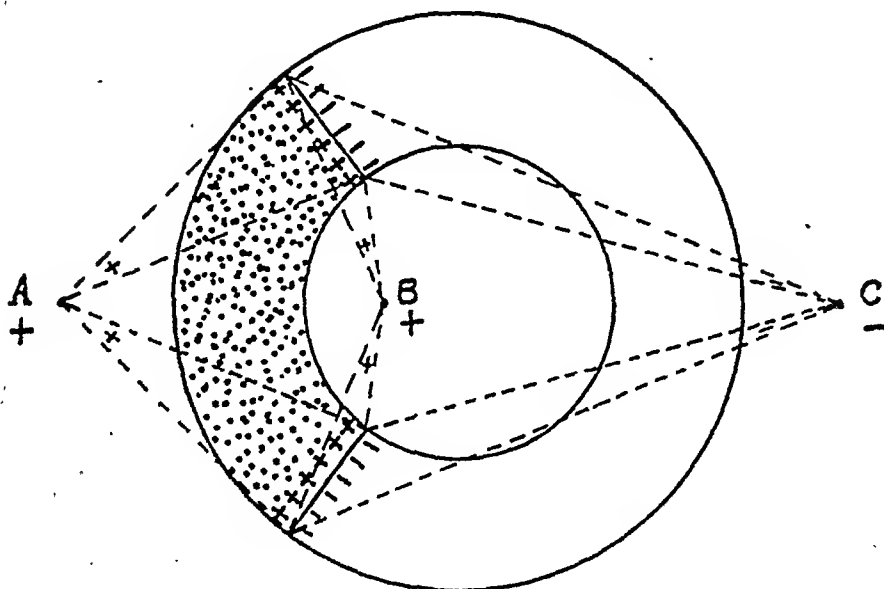


Fig. 11.—Diagrammatic representation of the electric field produced by an injury extending through the heart wall. This field is similar to one which would be produced if the injured muscle were polarized in the sense indicated. An electrode placed at a point adjacent to either the epicardial or endocardial aspect of the lesion would lie in a portion of the field where the potential was positive. An electrode placed at a point remote from the endocardial aspect of the lesion might lie in a portion of the field where the potential was negative.

lies just within the boundary between injured and uninjured muscle. In order to promote simplicity of description in the discussion which follows, the origin of the electric forces derived from an acutely injured muscle will be considered as located at this boundary. When an endocardial lesion is produced, a boundary of this kind is created, part of which is nearly parallel to the epicardial and endocardial surfaces, but there is another part which is more or less nearly perpendicular to these surfaces (Fig. 9). This latter part lies at the periphery of the lesion. Its breadth increases as the lesion is made deeper. During the inscription of the RS-T segment, the electric forces generated at this peripherally located boundary give rise to positivity at an exploring electrode placed on the epicardium at a point adjacent to the center of the lesion. These forces are opposed to those associated with the remaining parts of the boundary, which are parallel to the epicardial and endocardial surfaces. When the electrocardiograms reproduced in Fig. 10, *D* were recorded, the opposing forces apparently were of equal magnitude and the downward displacement of the RS-T segment present in the preceding electrocardiogram had disappeared. In the subsequent curves, the forces derived from the lateral aspects of the lesion apparently had a greater effect on the potential at the exploring electrode than those originating in the part of the boundary that was roughly parallel to the ventricular wall involved. With the production of the burn on the epicardium, another boundary parallel to the ventricular wall was created. Its orientation was such that the resulting forces opposed those associated with that portion of the boundary of the endocardial lesion which lay in a parallel plane. As a result, the forces produced at the peripheral portion of the boundary of the endocardial lesion gained the ascendancy and made the potential at the exploring electrode strongly positive. The RS-T segment was displaced upward and monophasic curves were recorded. A diagrammatic representation of this final stage is presented in Fig. 11.

Suppose that the distribution of boundaries defined in this diagram is an accurate representation of the situation which exists when an acute injury extends through the heart wall. Then an electrode placed on the endocardial surface of this transmural lesion should lie in a portion of its electric field where the potential is almost identical with that existing at an electrode placed on its epicardial surface. An experiment was designed to test this conclusion.

Experiment 7.—A large turtle was prepared in the usual manner. A lesion involving the endocardium on the left side of the ventricular cavity had been produced earlier in the experiment, but the electrocardiographic changes which had developed in the acute stage of that lesion had disappeared. The endocardial electrode was moved to the right side of the ventricular cavity and a set of electrocardiograms was recorded from the epicardial and endocardial electrodes. Through the endocardial electrode, the electrocoagulating current was applied in great strength for approximately five seconds. The white face of the burned tissue extended to the epicardium over an area 4 mm. in diameter. A series of electrocardiograms was recorded under circumstances described in the legend of Fig. 12.

Post-mortem examination revealed that the burn involved an area 8 mm. in diameter on the endocardial aspect of the wall of that portion of the ventricular cavity lying farthest to the right.

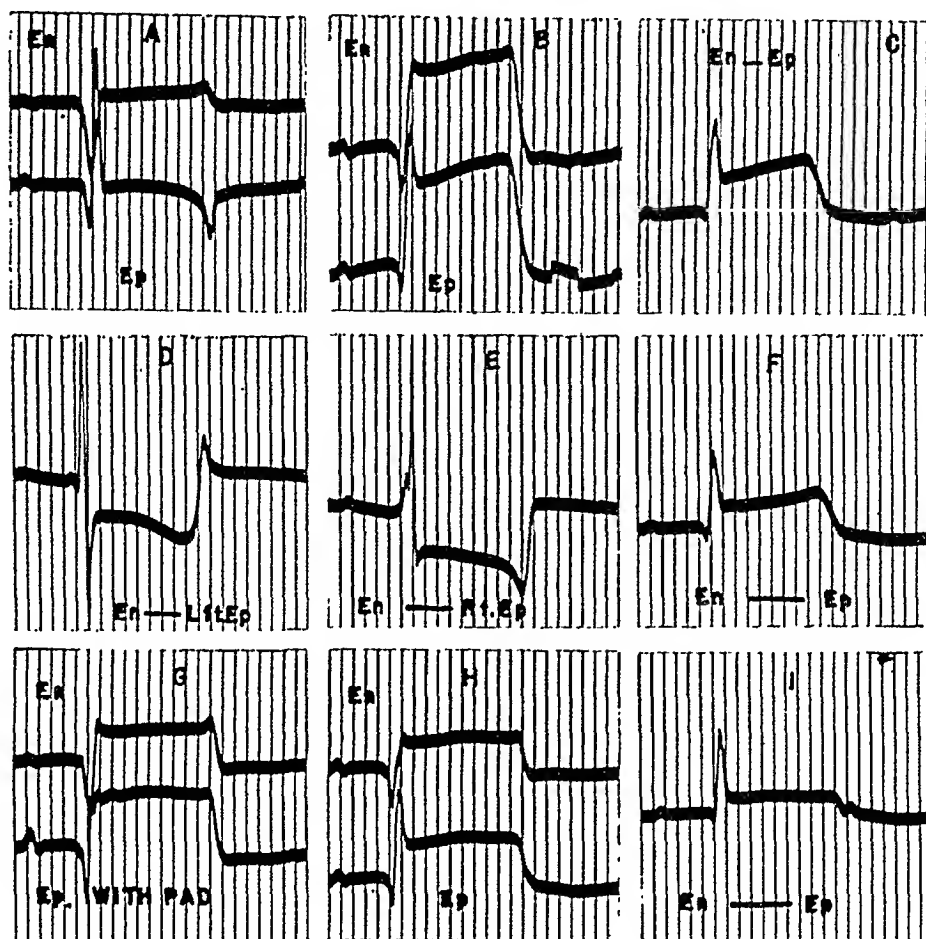


Fig. 12.—In all records where there are two curves, the upper one was derived from an electrode in the ventricular cavity (*En*) and the lower one from an electrode on the epicardial aspect of the right wide of the ventral wall of the heart (*Ep*). A, Control (ordinate scale: upper curve, 5 millivolts per centimeter; lower curve, 3.5 millivolts per centimeter); B, immediately after production of a burn extending from the endocardial to the epicardial aspect of the ventral wall of the heart on the right side, electrodes were in contact with the epicardial and endocardial aspects of the lesion (ordinate scale: upper curve, 2.5 millivolts per centimeter; lower curve, 3.5 millivolts per centimeter); C, epicardial electrode attached to left arm terminal of galvanometer and endocardial electrode to right arm terminal, lead selector set on Lead I (ordinate scale: 3.5 millivolts per centimeter); D, connections as in C, epicardial electrode moved onto uninjured muscle 8 mm. to left of lesion; E, connections as in C, epicardial electrode 3 mm. to right of lesion; F, epicardial electrode returned to site of lesion; G, pad soaked in Ringer's solution laid over ventral surface of heart, endocardial electrode on lesion and epicardial electrode on surface of pad at a point overlying the lesion (ordinate scale: upper curve, 2.5 millivolts per centimeter; lower curve, 1 millivolt per centimeter); H, pad removed from heart, endocardial and epicardial electrodes on respective surfaces of lesion (ordinate scale: both curves, 3.5 millivolts per centimeter); and I, connections, disposition of electrodes, and ordinate scales as in C.

The electrocardiograms recorded in Experiment 7 are reproduced in Fig. 12. They afford evidence that during inscription of the RS-T segment the potential was positive both at the epicardial and at the endocardial surface of the transmural lesion relative to the potential at a point remote from the heart. Covering the air-exposed portion of the ventral surface of the heart with a pad soaked in Ringer's solution produced certain changes in the electrocardiograms.

A reduction occurred in the amplitude of deflections recorded from the electrode placed on the surface of the pad at a point overlying the lesion. However, when the sensitivity was increased in that circuit in which the epicardial electrode was included, the curves recorded were quite similar to those obtained when the wick of the electrode rested on the surface of the lesion (Fig. 12, *G* and *H*).

The electrode on the epicardial surface of the lesion was attached to the left arm terminal and the electrode on the endocardial surface was attached to the right arm terminal of the same circuit. The lead selector switch was set on Lead I. The electrocardiograms reproduced in Fig. 12, *C* were then taken. With the connections described, the upward displacement of the RS-T segment indicates that the potential at the epicardial surface was positive relative to that at the endocardial surface. When the same connections were maintained and the epicardial electrode was moved off the surface of the lesion and onto uninjured muscle lying either to the right or to the left of the lesion, the potential at the epicardial electrode became negative relative to that at the endocardial electrode (Fig. 12, *D* and *E*).

These findings are compatible with those which would be anticipated if the significant electrical boundaries of the transmural lesion were disposed as is represented in Fig. 11. The fact that the potential of the epicardial surface of the lesion was positive to that of the endocardial surface rather than isopotential with it does not create a problem of significant proportions. In another experiment comparable to the one reported here, a lesion was produced which was less intense at the epicardial surface. The potential at the endocardial surface was then positive relative to that of the epicardium. The less pronounced positivity of the potential at the endocardial surface of the lesion in Experiment 7 was not the expression of a lesser intensity of injury on that aspect of the lesion. It may have been related to the complete desiccation of the tissues adjacent to the electrode with resultant alteration of the nature of the contact between the electrode and the cardiac surface.

A lesion extending through the ventricular wall from the epicardial to the endocardial surface has certain features in common with an infarct. In an attempt to define this relation more clearly, additional experiments were undertaken in which acute myocardial infarction was produced in dogs.

MYOCARDIAL INFARCTS

The chief characteristics of the electrocardiographic changes which commonly follow acute myocardial infarction either in man or in animals are well established. The explanation of these changes in terms of the dipole theory has been, on the whole, satisfactory and fruitful, but some perplexing problems presented by them are still unsolved. The facts indicate that a transmural infarct produces upward RS-T displacement in leads in which the exploring electrode faces the epicardial aspect of the involved wall. Changes of an inverse type are recorded in leads from an exploring electrode which faces the epicardial aspect of the uninvolved ventricular wall opposite the infarcted region. Thus, in infarction of the anterior apical portion of the left ventricle, upward RS-T dis-

placement occurs in electrocardiograms derived from an exploring electrode on a part of the thoracic wall which overlies the affected muscle. Such infarcts also commonly produce changes in the left arm potential, which result in upward RS-T displacement in leads from this extremity and in Lead I and downward displacement in Lead III. A unipolar lead from the left leg may show downward RS-T displacement. These changes which occur in anterior apical infarction are the inverse of those which develop during the acute stage of a posterior basal lesion.

The dilemma created by these findings has been defined by Bayley.² An acute subepicardial injury produces upward RS-T displacement in a lead from an exploring electrode which faces the affected portion of the ventricular wall. It is assumed that in this same lead an acute subendocardial injury would produce downward RS-T displacement. If the infarct is transmural and involves both the subepicardial and the subendocardial muscle, how then can the RS-T displacement so constantly associated with acute myocardial infarction develop? The problem becomes more perplexing if it is demonstrated that an infarct usually presents a more extensive surface on its endocardial than on its epicardial aspect. In the presence of such a lesion, the sum of the forces produced at the endocardial boundary would be greater than the sum of those produced at the epicardial boundary. Hence, downward RS-T displacement would be anticipated in a lead from an exploring electrode facing the epicardial surface of the infarct.

In his attempt to solve this problem, Bayley reviewed the studies of Mallory, White, and Salcedo-Salgar¹⁴ and of Karsner and Dwyer¹² which concern the pathologic changes of myocardial infarction. Mallory and associates reported that a layer of subendocardial muscle 0.3 to 0.5 mm. in thickness is preserved in the infarcted region. Bayley reasoned that if, during the acute stage of myocardial infarction, the muscle fibers in this subendocardial layer retained the physiologic properties of uninjured cells, then a boundary between uninjured and injured muscle would persist in the subendocardial zone of the ventricular wall. Consequently, the forces contributed to the electric field by the infarct would have the same orientation as those produced by a lesion confined to the subepicardial myocardium. If a subendocardial muscle layer is invariably preserved over all the infarcted portion of the ventricular wall, the kind of RS-T displacement usually observed in cases of coronary occlusion is satisfactorily explained.

In our discussion of lesions extending outward from the endocardial to the epicardial surface of the heart of the turtle, an account was given of a discrepancy which arose between the electrocardiographic phenomena anticipated and those recorded when a transmural lesion was produced. In our experiments the subendocardial tissues were injured. Such trauma as occurred within the subepicardial zone was transmitted through the underlying layers of the myocardium. Upward RS-T displacement was recorded not only in unipolar leads from the endocardial surface but also in unipolar leads from the epicardial surface of transmural lesions. We have suggested that the site of origin of the electric forces which produced these electrocardiographic effects was the boundary between injured and uninjured tissue at the periphery of the lesion. Irre-

spective of the validity of this hypothesis, the fact remains that an electrode placed on the epicardial aspect of an acutely injured region extending completely through the heart wall lies at a point in the electric field of that lesion where the potential is positive during the inscription of the RS-T segment. Preservation of a subendocardial muscle layer is not essential to the production of this particular feature of the usual electrocardiographic changes associated with acute myocardial infarction.

Our observations do not prove that a boundary between injured and uninjured muscle does not persist in the subendocardial zone of a myocardial infarct. Experiments designed to record the potential variations at the endocardial surface of an acutely infarcted region offer an approach to this problem likely to contribute relevant and significant data. If, at this stage of infarction, a layer of subendocardial muscle is preserved in a functional as well as in an anatomic sense, an electrode placed on the endocardial surface of the infarct would be at a negative potential with respect to an indifferent reference point during the RS-T period. If the subendocardial cells are injured so severely that no significant gradient of injury exists in this region, then at the endocardial surface as at the epicardial surface a relatively positive potential would develop at the end of the QRS interval (Fig. 11).

An experiment designed to record the potential variations at a point on or near the endocardial surface of an infarct is readily conceived. Its execution is attended by certain difficulties. The usual procedure for recording the potential within the ventricular cavity entails the introduction of a sharp-tipped electrode through the ventricular wall. The position of the tip of such an electrode can be estimated by simple measures with reasonable accuracy. However, production of an injury with the electrode itself must be avoided if a significant record of the potential changes in the cavity is to be obtained. For this reason, the tip of the electrode must not be pressed firmly against the endocardial surface of the infarcted region, but should be placed in proximity to that surface. The distance of the electrode from the endocardial surface determines its position in the electric field of the injured muscle. If this distance is not too great, the electrocardiographic changes recorded should be similar to, though of lesser magnitude than, those which would occur if the exploring electrode were in contact with the inner surface of the lesion.

Method.—Dogs weighing between 10 and 12 kilograms were used in these experiments. Anesthesia was induced with morphine and urethane. The pericardium was exposed either by splitting the sternum or by resecting the fourth, fifth, and sometimes the sixth rib on the left side. The pericardial sac was incised and its margins were sutured to the thoracic wall. A major branch of the left coronary artery was ligated by passing a suture under the artery and its vena comitans. When only temporary occlusion of the artery was desired, a wire was included in the ligature and only a single knot was tied. Removal of the wire and release of traction on the thread restored the flow of blood.

In the initial experiments, records were taken with the Sanborn Tribeam electrocardiograph. In later experiments the Einthoven galvanometer was used.

Because of technical difficulties, satisfactory electrocardiograms were secured in only the last five of the nine experiments. The electrode used for obtaining records from the epicardium was the relatively nonpolarizable soft-tipped device already described. A similar electrode was placed in contact with the subcutaneous tissues of the left hind leg and this served as the reference point for this lead when the Einthoven galvanometer was used. The electrode introduced into the ventricular cavity was of the filiform type described in the account of the experiments on turtles. The tip of this electrode was thrust through the ventricular wall in a region supplied by the artery to be ligated. Its shaft was sutured firmly to some portion of the adjacent thoracic wall. This electrode was highly polarizable. Hence it was essential that the resistance of the circuit in which it was included should be high. For this reason, the cavity electrode was connected to the grid terminal of a vacuum tube amplifier and thus indirectly to the galvanometer. The indifferent electrode for cavity leads was a copper disk 2 cm. in diameter, which was placed in contact with the subcutaneous tissues of the left hind leg. When leads from the electrode on the epicardial surface to the electrode in the ventricular cavity were used, the former electrode was attached to the left arm terminal and the latter to the right arm terminal of the galvanometer. The lead selector switch was then set on Lead I.

Results.—The electrocardiograms reproduced in Figs. 13, 14, and 15 were taken with the Einthoven galvanometer. They were obtained in the course of an experiment which was not wholly satisfactory in certain respects. In the first place, ligation of the anterior descending branch of the left coronary artery at a point 2 cm. below the tip of the left auricular appendage did not produce pronounced displacement of the RS-T segment either in the lead from the epicardial or in that from the endocardial side of a part of the ventral ventricular wall apparently supplied by this vessel. Only after ligation of the terminal branches of the circumflex division of the left coronary artery (Fig. 16) did more striking displacement of the RS-T segment develop. Secondly, because the region of infarction included only a limited portion of the myocardium at the apex of the left ventricle, the first electrode introduced into the left ventricular cavity did not lie opposite the center of the injured region. A second electrode, therefore, was introduced into this cavity at a point more centrally located relative to the infarct, but this was done only after the coronary vessels had been ligated and the resulting electrocardiographic changes had already developed.

In other respects the experiment was satisfactory. At the end of it, the heart was opened and the tips of both electrodes that had been introduced through the ventricular wall were observed to lie within the cavity of the left ventricle. The first electrode extended into this cavity a distance of 8 mm. and the second, a distance of 4 millimeters. A small thrombus 3 mm. in diameter had formed around that portion of each electrode which projected beyond the inner surface of the ventricular wall. Except at the points of entrance, no gross endocardial injury produced by the electrodes could be identified.

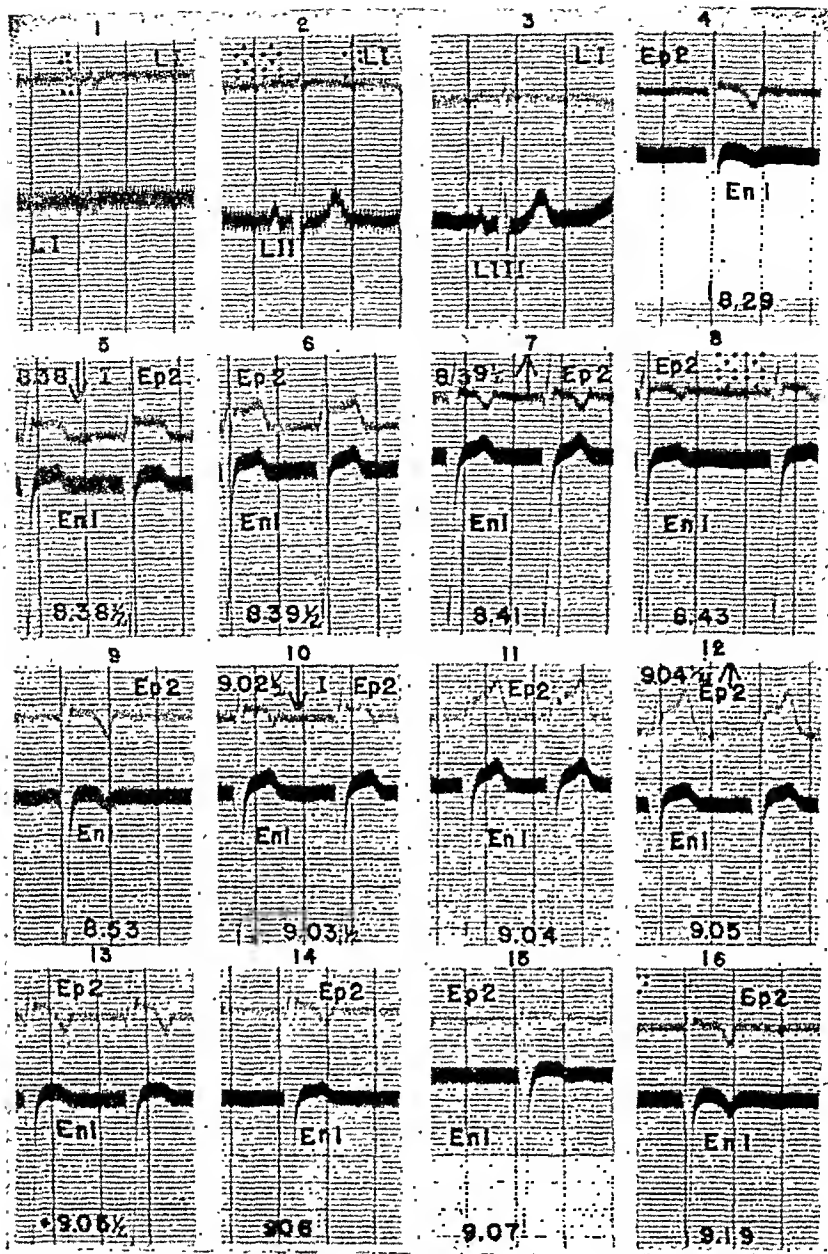


Fig. 13.—Ordinate scale: in standard limb leads, 1 millivolt per centimeter; in direct leads from ventricular surface or cavity, 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
1	8:00	Lead I	Lead I
2	8:02	Lead I	Lead II
3	8:04	Lead I	Lead III
4	8:29	Point 2 (see Fig. 16)	Point 1
5	8:38 1/2	Occlusion at I (see Fig. 16) for 90 seconds	
6	8:39 1/2	Point 2	Point 1
7	8:41	Point 2	Point 1
8	8:43	Point 2	Point 1
9	8:53	Point 2	Point 1
10	9:02 1/2	Occlusion at I for 105 seconds	
11	9:03 1/2	Point 2	Point 1
12	9:04	Point 2	Point 1
13	9:05	Point 2	Point 1
14	9:05 1/2	Point 2	Point 1
15	9:06	Point 2	Point 1
16	9:07	Point 2	Point 1
	9:19	Point 2	Point 1

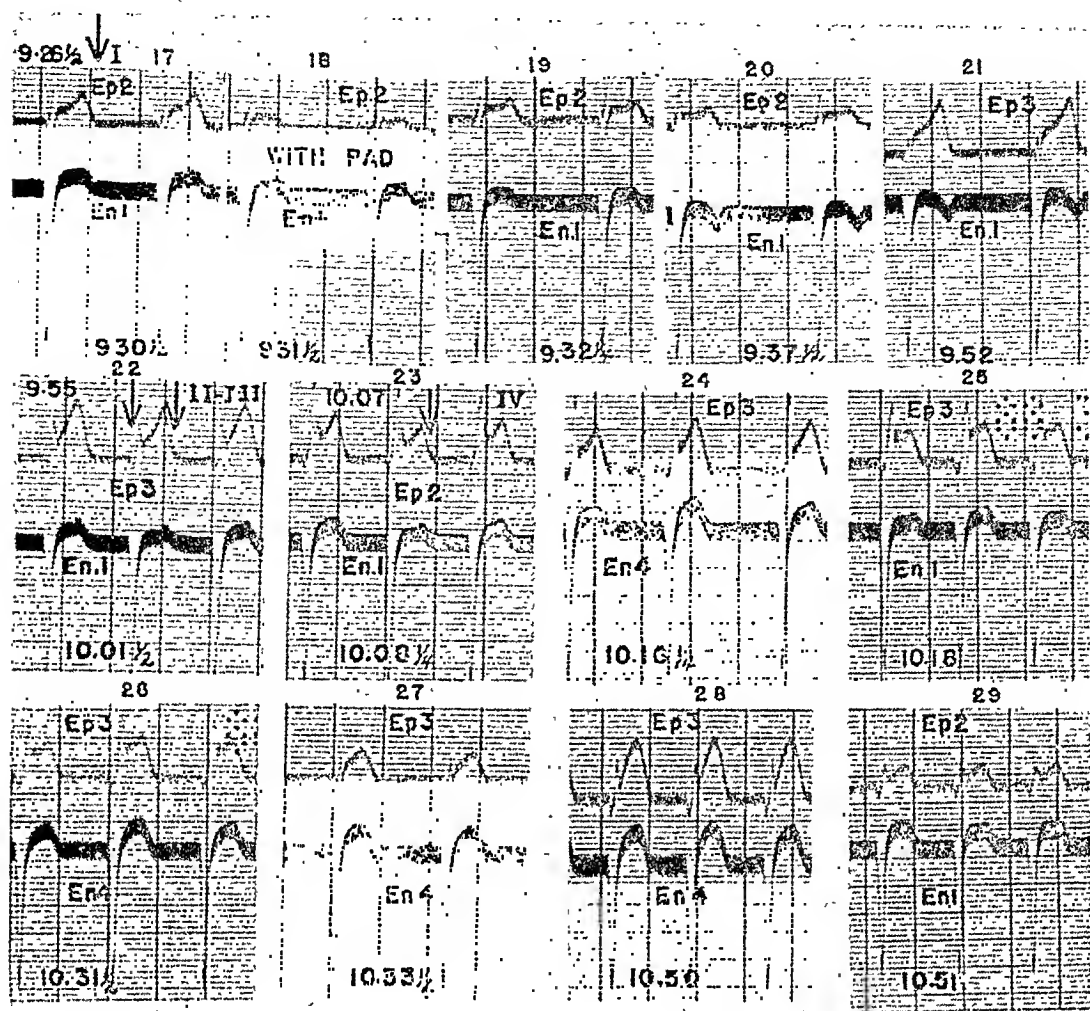


Fig. 14.—Ordinate scale: 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
	9:26 1/2	Occlusion at I (see Fig. 16) permanently	
17	9:30 1/2	Point 2 (see Fig. 16)	Point 1
18	9:31 1/2	Point 2 with pad	Point 1
19	9:32 1/4	Point 2	Point 1
20	9:37 1/2	Point 2	Point 1
21		Point 3	Point 1
	9:55	Occlusion at II and III permanently	
22	10:01 1/2	Point 3	Point 1
	10:07	Occlusion at IV permanently	
23	10:08 1/4	Point 2	Point 1
24	10:16 1/4	Point 3	Point 4
25	10:18	Point 3	Point 1
26	10:31 1/2	Point 3	Point 4
27	10:33 1/2	Point 3 with pad	Point 4
28	10:50	Point 3	Point 4
29	10:51	Point 2	Point 1

Analysis of the electrocardiograms in Figs. 13, 14, and 15 should not be extended to exact quantitative determinations. After the first of the standard limb leads had been taken, the sensitivity of the galvanometer was readjusted and it was not altered again throughout the remainder of the experiment. It should be recognized, however, that other factors affected the magnitude of the

deflections in the electrocardiograms taken. The electrode on the endocardial aspect of the lesion probably was not in contact with the ventricular wall. The distance of this electrode from the endocardium may have varied during the contraction of the ventricle and as a result of the rhythmic inflation and deflation of the lungs. The size of the deflections in leads from the epicardial electrode was reduced whenever a small amount of free fluid accumulated about

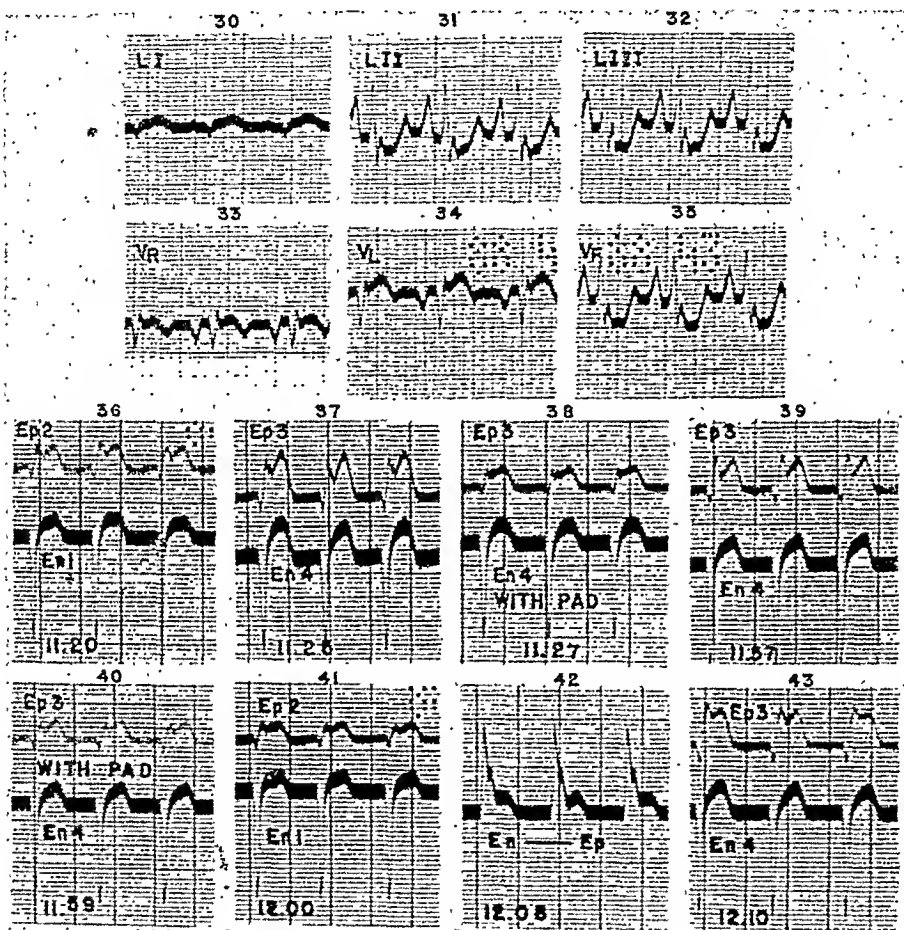


Fig. 15.—Ordinate scale: in standard limb leads, 1 millivolt per centimeter; in direct leads from ventricular surface or cavity, 20 millivolts per centimeter.

Curve	Time	Upper curve Site of epicardial electrode	Lower curve Site of endocardial electrode
30			
31	10:55		Lead I
32			Lead II
33			Lead III
34	11:05	Unipolar lead, right foreleg	
35		Unipolar lead, left foreleg	
36	11:20	Unipolar lead, left hindleg	
37	11:25	Point 2 (see Fig. 16)	Point 1
38	11:27	Point 3	Point 4
39	11:57	Point 3 with pad	Point 4
40	11:59	Point 3	Point 4
41	12:00	Point 3 with pad	Point 4
42	12:05	Point 2	Point 1
43	12:10	L. A. terminal at epicardial point 3; R. A. at endocardial point 4	Point 4

the tip of this electrode. Therefore, while the magnitude of the RS-T displacement in the electrocardiograms of this series is of some interest, we shall emphasize only its direction, which is of greater significance.



Fig. 16.—Diagram of heart indicating points to which reference is made in legends of Figs. 13, 14, and 15.

In Fig. 13, curves 5 to 9, are represented the electrocardiographic changes associated with, and sequential to, temporary occlusion of the anterior descending branch of the left coronary artery. During this initial procedure the occlusion was maintained for ninety seconds. Upward displacement of the RS-T segment developed in leads from the electrode placed on the epicardium. The magnitude of this displacement was not great. In leads from the endocardial electrode, the inverted T wave became upright and this change was accompanied by a slight upward shift in the RS-T level. These phenomena appeared within thirty seconds after occlusion of the artery and regressed with almost equal speed.

Twenty-four minutes after the first occlusion of the artery, traction was again placed on the ligature and was maintained on this occasion for 105 seconds (Fig. 13, curves 10 to 16). The changes during this period of ischemia were slightly more pronounced in leads from both the epicardial and the endocardial electrodes. In other respects, the developments were like those which followed the initial occlusion.

Twenty-four minutes later the ligature was tied permanently (Fig. 14, curve 17). The electrocardiographic changes which appeared during the first few minutes after this occlusion simulated those occurring in the preliminary periods of ischemia. However, after five minutes there was some decrease of the upward displacement of the RS-T segment in leads from both the epicardial and endocardial electrodes, particularly in the latter (Fig. 14, curve 19). In the

21), the epicardial electrode was shifted to a point nearer the center of the injured region; the position of the endocardial electrode was not changed.

Twenty-nine minutes after the final ligature had been placed on the anterior descending branch of the left coronary artery, the first of the terminal branches of the left circumflex artery was occluded (Fig. 14, curve 22). Twelve minutes later, the third and last ligature was placed around one of these branches (Fig. 14, curve 23). Fifty minutes after the first permanent occlusion, an electrode was introduced into the left ventricular cavity at a point near the center of the injured myocardium and an electrocardiogram was recorded from this lead (Fig. 14, curve 24). Between ninety and 120 minutes after the first permanent occlusion, the degree of elevation of the RS-T segment was maximal in both the epicardial and the cavity leads. It was at this time when the potential at two points on the endocardial aspect of the injured muscle was positive during inscription of the RS-T segment that the standard limb leads and the unipolar extremity leads were recorded. The presence of downward displacement of the RS-T segment in the unipolar lead from the left hind leg at a time when cavity leads displayed upward RS-T displacement is of particular interest.

One of the last electrocardiograms in the series (Fig. 15, curve 42) records the potential difference between the electrode placed near the center of the epicardial aspect of the infarcted tissue and an electrode in the ventricular cavity 3 or 4 mm. from the inner surface of the same part of the infarct. The upward displacement of the RS-T segment in this lead indicates relative positivity of the epicardial electrode at the end of the QRS interval. However, the degree of positivity of the epicardial relative to the endocardial electrode was less than the degree of positivity of the epicardial electrode relative to an electrode placed at a point remote from the heart (Fig. 15, curve 43).

Finally, attention may be directed to one other observation which concerns the magnitude rather than the kind of electrocardiographic alterations which developed. In many of the curves reproduced in Figs. 13, 14, and 15, electrical alternans is present. This phenomenon is most obvious in curve 23 of Fig. 14. Examination of these curves reveals that when upward displacement of the RS-T segment was greater in the epicardial electrocardiogram, it was likewise greater in the lead from the endocardial electrode. If the electric forces responsible for this displacement arose at a boundary which lay between the epicardial and endocardial surfaces, greater positivity on one side of the ventricular wall should have been accompanied by greater negativity on the other. If, on the other hand, the electric forces in question originated at the periphery of the lesion, an increase in their magnitude would have a similar effect on the potential of both surfaces of the ventricular wall and, therefore, on that of both electrodes.

The observations presented here illustrate a series of experiments which was incomplete. In particular, studies should have been made of the changes of potential within the left ventricular cavity following ligation of the circumflex branch of the left coronary artery. One attempt to do this was made but the results of this experiment could not be interpreted precisely because of inadequate information regarding the position of the endocardial electrode.

In summary of the available data on the electrocardiographic effects of experimental myocardial infarction, the following statements may be made. In experiments on dogs, the artery or arteries supplying the anterior apical portion of the left ventricle were ligated and the potential changes within the left ventricular cavity were recorded. The tip of the exploring electrode was placed in this cavity at a point near the center of the injured region of the adjacent myocardial wall. During the RS-T interval, the potential at the tip of the cavity electrode was positive relative to the potential at an electrode placed at a point remote from the heart. This positivity at the endocardial aspect of the lesion existed in the presence of changes typical of anterior apical infarction in leads from the epicardial surface of the lesion, in the standard limb leads, and in the unipolar extremity leads.

The results of our experiments do not justify the conclusion that the electric forces responsible for RS-T displacement in acute myocardial infarction always arise at boundaries which define the peripheral limits of the lesion. We may add that the application of concepts derived from experiments in which the blood supply of some part of the healthy canine myocardium was suddenly cut off to the interpretation of what takes place when the nutrition of the human heart is disturbed by thrombosis of one of its sclerotic arteries must always be accomplished with due regard for the possibility of error. To assume that the results of our experiments can be applied to all cases of myocardial infarction in man would be premature.

Having accorded these considerations the recognition which they merit, we may make the following statements without elaboration of their implications. A boundary between injured and uninjured muscle must define all or part of the peripheral limits of every myocardial infarct. Since the left ventricle is conical and since extension of a zone of infarction to its basal border would not produce a junction between injured and uninjured muscle in this region, the combined areas of the apical and basal boundaries of the infarct may be small in comparison with the areas of its other boundaries. In a heart which is not dilated, the area of the boundaries at the periphery of the infarct may approach the area of the endocardial aspect of the injured tissue. This would be most likely to happen during ventricular systole. At this time, the size of the ventricular cavity is decreased and the thickness of the ventricular walls is increased. It is during systole that the RS-T segment is inscribed.

SUMMARY AND CONCLUSIONS

The modifications of the RS-T segment of the ventricular complex produced by acute lesions of various types were recorded in a series of experiments on turtles and dogs.

In experiments on turtles, it was found that when the ventral surface of the heart was exposed to air an acute injury involving only the outer layers of the exposed ventricular wall produced upward RS-T displacement in unipolar leads from the epicardial surface of the affected region but, as a rule, did not produce downward RS-T displacement in leads from an adjacent portion of the ven-

tricular cavity. Downward RS-T displacement did occur in such cavity leads when the ventral epicardial surface was in contact with a conducting medium.

When a lesion involved the same part of the ventricular wall but was confined to the subendocardial muscle layers, the RS-T displacement was upward in leads recorded from an adjacent part of the ventricular cavity and in leads from the epicardial aspect of the ventricular wall opposite the damaged portion of the myocardium. RS-T displacement was downward when the exploring electrode was placed on the epicardial aspect of the affected ventricular wall.

When, in experiments on turtles, a lesion involving both the inner and outer layers of the ventricular wall was produced by electrocoagulation, upward RS-T displacement was recorded in leads from either the epicardial or the endocardial aspect of the region of injury. Similarly, when acute myocardial infarction was produced in the anterior apical portion of the canine heart by coronary ligation, the RS-T displacement was upward in leads from a portion of the ventricular cavity adjacent to the injured muscle and in curves recorded with the electrode on the epicardial surface of the region of infarction. The electric forces responsible for upward RS-T displacement on both aspects of these transmural lesions were attributed to the boundaries between injured and uninjured muscle at the peripheral margins of the lesion.

Muscle juice, probably because of its high potassium content, produces maximal RS-T displacement when it is placed on the ventricular surface.

An attempt has been made to interpret these observations in terms of the dipole theory as it applies to the electrocardiographic consequences of acute myocardial injuries.

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THE VARIED CLINICAL SYNDROMES PRODUCED BY DISSECTING ANEURYSM

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PHILADELPHIA, PA.

A GENERATION ago when Herrick¹⁻³ and Levine and Tranter⁴ first reported their fundamental observations in acute thrombosis of the coronary arteries, the ante-mortem diagnosis of myocardial infarction was a medical rarity. Today myocardial infarction is a medical condition readily recognized by most physicians. We believe a somewhat analagous situation exists with reference to the diagnosis of dissecting aneurysm of the aorta. The various clinical syndromes produced by this disturbance are gradually becoming clarified. Physicians are not only beginning to recognize the condition in patients who do not survive, but are suspecting its presence in patients who have survived the accident and recovered.

Willius and Cragg⁵ listed as reasons for the failure to make the diagnosis of dissecting aneurysm: (1) The relative infrequency of the condition; (2) the absence of a characteristic syndrome; (3) the limitation of special diagnostic adjuncts; and (4) universal lack of clinical suspicion. We feel the last of these is perhaps the most important. There has been an increase in accurate diagnosis during the past decade, but Reich⁶ has stated that "it is only through relentless correlation of post-mortem findings with the clinical picture in individual cases, that a true clinical consciousness of the disease can be adequately established."

In the forty-four cases that are the basis of this report (eleven were diagnosed ante mortem), an attempt will be made to emphasize some of the features that should enable one to make a clinical diagnosis of dissecting aneurysm.

CLINICAL FEATURES

Incidence.—Until we learn to recognize recovered cases of dissecting aneurysm, we will not be able to arrive at an approximation of the true incidence of dissecting aneurysm. We have seen at least two cases that we feel are instances of healed dissecting aneurysm. Weiss and co-workers⁷ believed that one out of ten patients recover, and die of other causes. This was found to be the case in two of our cases at necropsy.

Mote and Carr,⁸ in a five-year study from the coroner's office in San Francisco, found that 1.1 per cent of all cases of sudden death were due to dissecting aneurysm. They emphasized that there was a greater incidence in coroners'

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offices than hospital records would indicate, because death might be so sudden that hospitalization was not possible. Gouley⁹ has found dissecting aneurysm to be one of the commoner causes of sudden death in Philadelphia. He found the incidence to be one in every 480 autopsies on patients beyond the age of 20 years.¹⁰ Glendy and associates¹¹ found nineteen cases in 8,200 autopsies at the Massachusetts General Hospital over a thirty-eight-year period, an incidence of one in every 431 autopsies.

Age and Sex.—Interest in dissecting aneurysm of the aorta was stimulated by the excellent monograph written by Shennan¹² in 1933. He added seventy-five instances of dissecting aneurysm collected throughout England to those already reported, making a total of 302 proven cases. Over 80 per cent of these occurred in subjects over 50 years of age; 65 per cent were in men. A similar incidence is found in the forty-four cases we are reporting (Table I). They ranged in age from 35 to 82 years, with the majority occurring in the fifth and sixth decades. Of the forty-four cases, 67 per cent were in men. This experience conforms to the generally accepted opinion concerning the age and sex incidence of dissecting aneurysm. However, attention must be paid to the data presented by Schnikter and Bayer.¹³ In reviewing the literature up to 1943, they were impressed with the occurrence of this condition in younger people. In the 580 cases they accepted as proven cases of dissecting aneurysm gathered from the world's literature, 141, or 24 per cent, occurred in individuals less than 40 years of age. Of those cases occurring in women, approximately 50 per cent were seen during pregnancy.

TABLE I. AGE AND SEX INCIDENCE OF DISSECTING ANEURYSM

AGE	SEX		TOTAL	
	MALE	FEMALE	NUMBER	PER CENT
30-39		2	2	4.5
40-49	3	1	4	9.0
50-59	12	4	16	36.3
60-69	10	3	13	29.8
70-79	3	4	7	15.9
80-89	1	1	2	4.5
	29	15	44	

Symptomatology.—Many observers^{6,7,11-16} have published excellent clinical descriptions of the symptoms encountered. As a rule the patient is suddenly seized with a severe tearing or ripping pain in the chest or precordial area, or upper abdomen. Collapse, sudden unconsciousness, or death may then ensue. If consciousness is retained, the pain may increase greatly in intensity. It may

radiate to the shoulder, back, abdomen, renal area, or groin. The radiation of the pain will depend to some extent on the direction of the dissection, and the various organs involved. The time relations of the various types of pain may be of help in the differential diagnosis of dissecting aneurysm. The pain may be so intense that repeated injections of narcotics fail to give relief. In many cases, however, there may be no history of pain whatsoever. There have been reported^{11,13,17,18} cases in which pain was absent during the entire course of the illness. In twenty-four of our forty-four cases there was no recorded history of pain at any time during the patient's illness (Fig. 1).

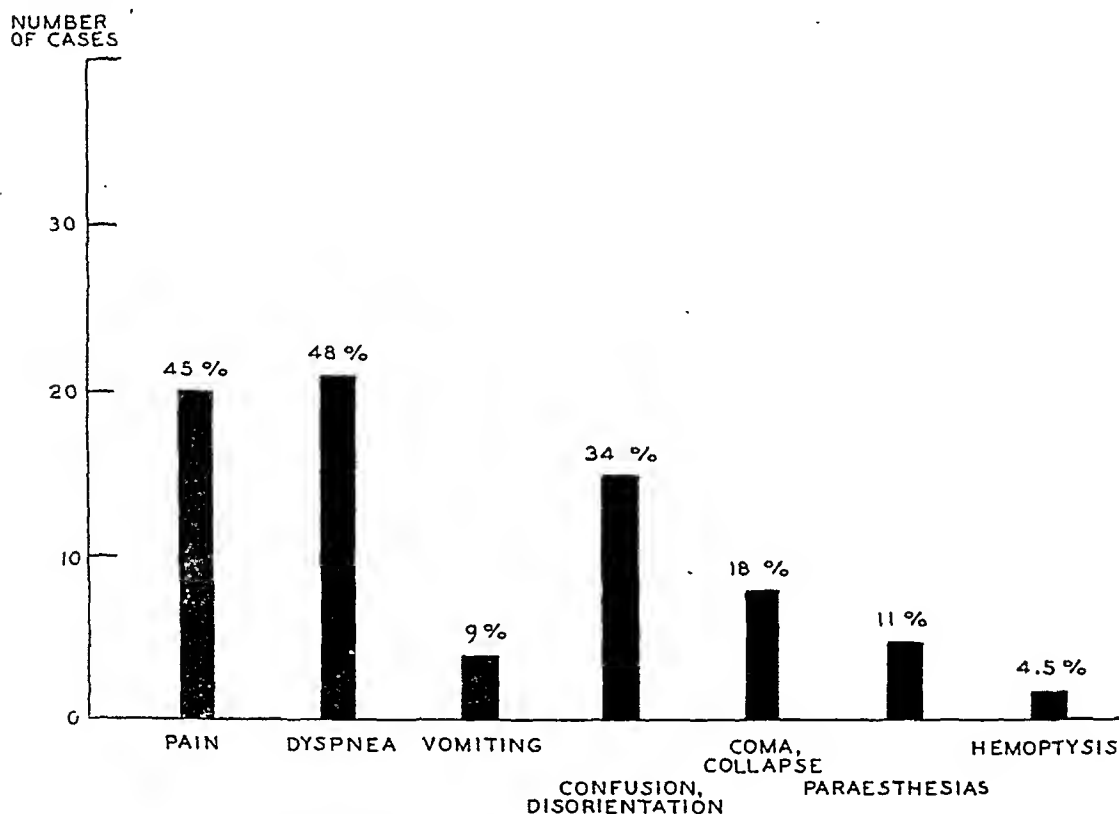


Fig. 1.—Symptomatology in forty-four cases of dissecting aneurysm.

Dyspnea was also an important symptom. It is understandable why so many cases, particularly those occurring in older individuals, with dyspnea and without pain are considered cardiac in origin and are not recognized as cases of dissecting aneurysm.

We were impressed with the number of times that neurological disturbances played a large part in the symptomatology. The shock occurring with the tearing of the aorta may be so severe that syncope or collapse develops. In some cases, the only history obtainable was that the patient was found in coma. In other instances agitation, disorientation, convulsive seizures, or bizarre peripheral neurological signs may cause one to look to the cerebrum or spinal cord as the primary source of the trouble.

Physical Findings.—The physical findings will vary greatly, depending upon the length of time the patient survives, the age of the patient, the preexisting cardiovascular disturbance, and the vessels and organs involved in the dissection. If the patient survives the initial aortic tear, fever, tachycardia, and tachypnea usually develop (Fig. 2).

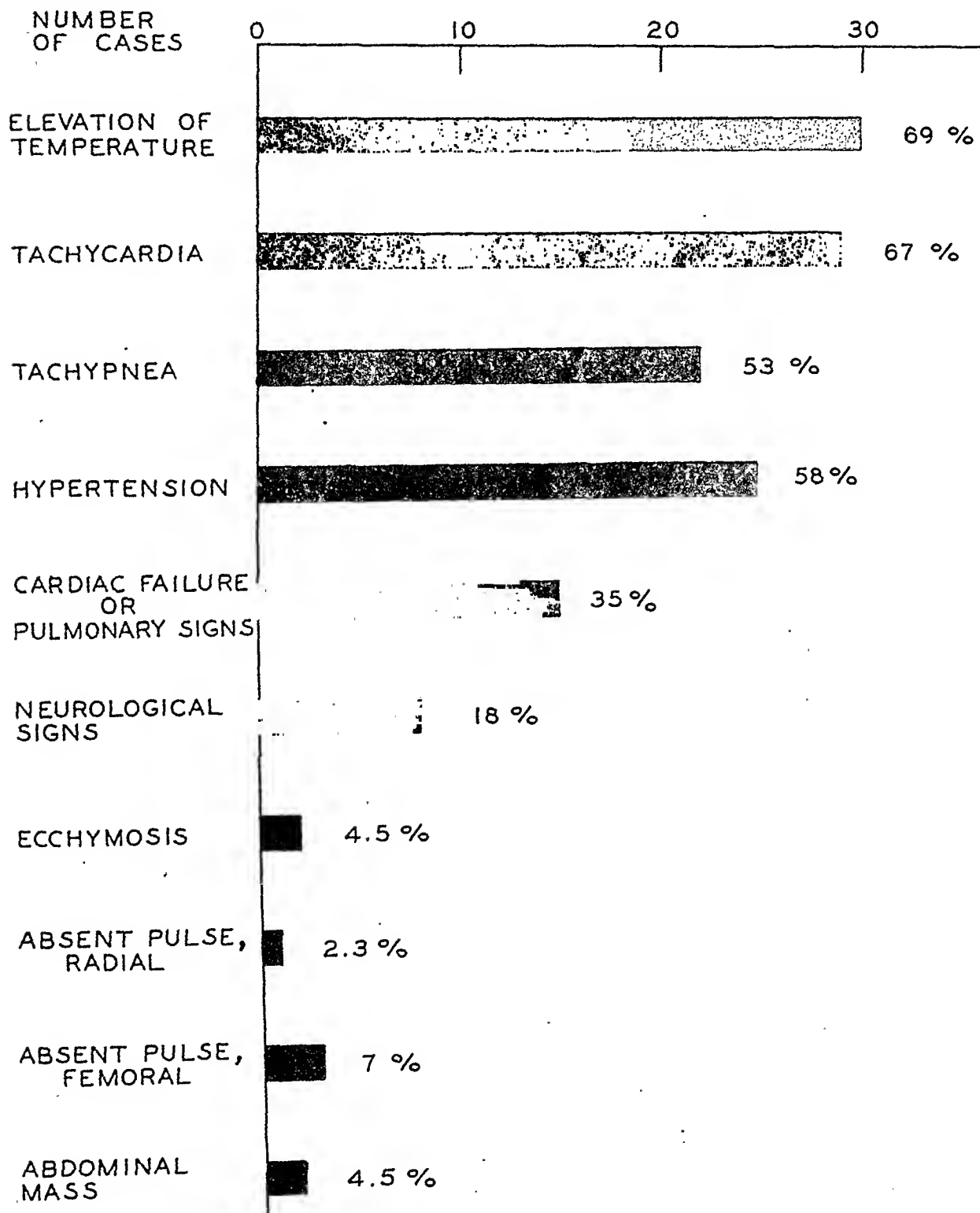


Fig. 2.—Physical findings in forty-four cases.

Hypertension is frequently present, but the question of the hypertensive background of dissecting aneurysm is still quite controversial. Mote and Carr,⁸ Schnikter and Bayer,¹³ Hamburger and Ferris,¹⁷ and Rogers¹⁹ have all stated that there may be no history of hypertension. In the forty cases in which a blood pressure was recorded in our series, systolic pressures of 150 mm. Hg or more were found in twenty-five instances. Systolic pressures ranged from 70 to 300 mm. Hg, and in one case the pressure was 130 mm. higher in the right than in the left arm. Diastolic pressures ranged from 30 to 130 mm. of mercury. A few cases with hypotension developed hypertension before they died, but the reverse also occurred. It is, of course, quite possible that some patients with low or normal pressures on admission had hypertension before aortic rupture occurred. There seems no question, however, that some cases, particularly those in younger individuals, fail to present evidence of hypertension in the history or physical examination or at necropsy.

Cardiac enlargement, signs of cardiac failure, various cardiac murmurs, gallop rhythm, or a pericardial rub may all be found (Table II). It is these signs particularly that direct our attention toward the heart, suggesting the diagnosis of cardiac failure or myocardial infarction rather than dissecting aneurysm.

One important sign that may be almost pathognomonic of dissecting aneurysm is the development of the diastolic murmur of aortic regurgitation. Gouley and Anderson,¹⁰ Resnik and Keefer,²⁰ Hamman and Apperly,²¹ Zimmerman,²² and Wainwright²³ have all called attention to this finding, particularly in chronic cases. The murmur is apparently due to dilatation or deformity of the aortic ring, resulting from the dissection. When sought for diligently, its discovery may enable one to make the diagnosis in suspected cases.

TABLE II. CARDIAC FINDINGS RECORDED IN FORTY-FOUR CASES

Cardiac enlargement		8
Gallop		2
Friction rub		2
Auricular fibrillation		2
Murmurs	Aortic systolic	10
	Aortic diastolic	6
	Mitral systolic	12
	Mitral diastolic	4

Signs of cardiac failure, pulmonary consolidation, or pleural effusion occurred in fifteen cases. These signs were usually more marked in the left hemothorax. On five occasions bloody pleural fluid was obtained on aspiration.

Some of the most bizarre findings are those suggestive of neurological involvement. Particular attention has been paid to this topic by Niehaus and

Wright,¹⁸ Rogers,¹⁹ and Weisman and Adams.²⁴ Patchy and bizarre vascular or neurological findings may be obtained with or without pain. These varied signs, most marked as a rule in the legs, are due to the circulatory deficiencies resulting from involvement of the intercostal, lumbar, or femoral arteries. The dissection may produce a periarterial sympathectomy. Or involvement of an anterior spinal artery may result in a sudden painless paraplegia. Weisman and Adams²⁴ made a detailed study of the neurological findings in thirty-eight cases of dissecting aneurysm. The diagnostic accuracy was greatly increased in those cases in which the neurological findings predominated.

Laboratory Findings.—Many of the patients did not live long enough for detailed laboratory studies to be made. Leucocytosis was a frequent finding, with an increase particularly in the polymorphonuclear leucocytes. If the bleeding (into the aorta, pericardium, or pleura) is extensive enough, severe progressive anemia may develop in a few hours. The urine may show a trace to a cloud of albumin. If dissection has approached or involved the renal arteries, hematuria or even uremia may predominate in the symptom complex.

Electrocardiograms were available for study in twenty-three cases. It is difficult to evaluate the changes found. This is particularly so when we realize that the major portion of these individuals usually had severe vascular disease before their dissecting aneurysm developed. Many previously had had one or more myocardial infarctions. It would be expected, therefore, to find abnormal electrocardiograms in most of these patients. Changes of the QRS complex, S-T segment, and T waves were present in almost all of the tracings. The changes, however, were not specific enough to consider the electrocardiogram as diagnostic of dissecting aneurysm. In three of our cases, patterns suggestive of acute myocardial infarction were obtained. At necropsy, myocardial infarcts due to involvement of the coronary arteries by the aortic dissection were found. A number of authors have reported cases in which the electrocardiograms resembled those found in acute myocardial infarction, without an infarct being demonstrable post mortem. In one of our cases, an electrocardiogram indicative of acute pericarditis, plus a bloody pericardial tap, led to an ante-mortem diagnosis of dissecting aneurysm. By and large, however, the electrocardiographic changes are non-specific and merely indicate the presence of some myocardial or pericardial derangement.

Roentgen examination may also be of some help in the differential diagnosis. Wood and associates²⁵ have described these signs in detail. They consist of deformity of the aortic or supracardiac shadow. This may gradually or rapidly increase in size. In Case 9, for example, gradual progressive increase in the size of the aorta over a period of one year was the sign which led one of our colleagues to make a diagnosis of dissecting aneurysm of the aorta months before death ensued.

Pathologic Aspects.—Discussion of the various pathologic features underlying dissecting aneurysm of the aorta have been published by Shennan,¹² Moritz,²⁶ Klotz and Simpson,²⁷ Schätttenberg and Ziskind,²⁸ Leary and Weiss,²⁹ and Sailer.³⁰ Readers are referred to these articles for detailed consideration of

the pathologic features of dissecting aneurysm. Some authors continue to adhere to the theory that rupture begins in the intima at or close to the margin of an atheromatous ulcer. The pressure of the column of blood then is supposed to carry the dissection into and along the media. Peery³¹ has described an incomplete tear of the aorta that he thought might be the possible precursor of dissecting aneurysm.

Most observers, however, describe the process somewhat as follows: The primary change in the aorta is a cystic degeneration of the media (so-called Erdheim's medionecrosis cystica). The cause of this degeneration is not certain: In this type of aorta, there occurs a rupture of one or more medial nutrient vessels into one of the cystic spaces, producing a hematoma. The hematoma enlarges, splitting the layers of the media, and the intima is then secondarily torn. An opening is thus made into which the large aortic column of blood may force itself and produce varying degrees of dissection along the medial coat. The dissection, which begins in the ascending aorta in over 70 per cent of the cases, may also extend cuspsward. Some writers feel that dissection backward toward the cusps is responsible for distortion of the aortic ring and the resultant diastolic murmur that is such a valuable diagnostic sign.

An additional pathologic finding that occasionally may be the basis of dissection is hypoplasia or coarctation of the aorta. Schnikter and Bayer¹³ and Reifstein and associates³² in particular have discussed this. Schnikter and Bayer¹³ suggested that if dissecting aneurysm occurred in individuals before the age of 40 years, there was a strong probability that hypoplasia or coarctation of the aorta would be found at necropsy. They cited Maude Abbott's statistics, in which thirty-three of her 200 cases of coarctation of the aorta died of dissecting aneurysm.

Irrespective of the pathologic basis of the dissection, the length of time that the patient survives after the initial catastrophe will determine the further clinical and pathologic findings. The shock may be so severe that death is instantaneous. Or the progress of the dissection may be slower, and the process advance along the aorta. If the great vessels arising from the arch are involved, cerebral symptoms may predominate; or the dissection may involve the spinal arteries, yielding an "anterior spinal artery thrombosis syndrome." Beyond this the gastrointestinal vessels may be involved, and gangrene of the bowel or mesenteric thrombosis ensue. Frequently, one or the other renal artery is involved, and hematuria or renal infarction results. In an occasional case the entire abdominal aorta has been involved, so that at necropsy the basis of a saddle or femoral thrombosis with gangrene of the leg was found to be a dissecting aneurysm beginning in the thoracic or abdominal aorta.

If death does not result from shock, the terminal event is most apt to be rupture into the pericardium. In other instances, rupture may be into the pleural cavity, particularly the left. In an occasional case, especially one lasting for sometime, death may be due to cardiac failure. As a matter of fact, this was the mode of death in almost 50 per cent of the sixty-six cases listed as "chronic dissecting aneurysm" by Shennan.¹²

We must not lose sight of the fact that dissecting aneurysm is not invariably fatal. Weiss⁷ felt that one out of ten cases of dissecting aneurysm heal, and that "dissecting aneurysm of the aorta may be compatible with good health for many years, and death result from other causes." A number of cases^{7,16} have been reported in which dissection resulted in a double-barrelled aorta. The patients lived long enough to develop deep atheromatous changes in the new aortic wall. This occurred in two of our cases.

DISCUSSION

As interest in the question of dissecting aneurysm increased, hospital necropsy records²³ and individual reports³⁴⁻⁴⁰ of verified cases diagnosed ante-mortem accumulated. It became apparent that the condition was neither as rare nor as difficult to diagnose as it was first considered to be. We have not attempted to completely review all the pertinent literature; extensive bibliographies can be found in a number of papers. To date there must be almost 650 cases on record, including those reported in this presentation. Whereas, in only six of Shennan's 302 cases was the diagnosis suspected before death, with the eleven cases that we are including there are reports of at least sixty cases which were diagnosed clinically.

We have attempted to correlate the various clinical and pathologic studies reported with the findings in our cases. Depending on the group of symptoms presented, dissecting aneurysms that do not produce sudden death can be divided roughly into the following five clinical types.

Cardiovascular.—This is by far the largest and most important group. In nineteen of our forty-four cases, the primary ante-mortem diagnosis referred to the cardiovascular system (Table III). They were considered as cases of hypertensive or arteriosclerotic heart disease, or simply cardiac failure. Acute myocardial infarction was diagnosed in four cases, and considered as a possibility in four of the eleven cases diagnosed correctly. This difficulty in differential diagnosis is quite understandable. Hypertension, chest pain, evidence of cardiac failure, a pericardial friction rub, or the various physical signs of cardiac involvement previously referred to all contribute to a diagnosis of hypertension, cardiac failure, or acute myocardial infarction. In cases of "chronic dissecting aneurysm," as discussed by Gouley and Anderson¹⁰ and Shennan,¹² marked cardiac enlargement may result. Finally, intractable cardiac failure may occur, and little basis remain for venturing a diagnosis of dissecting aneurysm.

In an occasional case, the clinical picture may closely simulate primary iliac or femoral thrombosis and little attention be given to the possibility of an underlying thoracic or abdominal dissecting aneurysm.

Cerebral.—In ten of our cases the final ante-mortem diagnosis was cerebral vascular accident. We have already referred to the importance of the cerebral and neurological findings. Particularly is one apt to think of a cerebral accident if the patient is admitted in confusion or coma, without a history of antecedent pain. The peripheral neurological signs may also focus the attention on the cerebrum or spinal cord.

Pulmonary.—The pulmonary signs may be marked. A number of cases have been diagnosed as pneumonia and given chemotherapy or antibiotics. In some patients, thoracentesis was done for suspected cardiac or tuberculous effusion. Left hemothorax should always lead to the suspicion of dissecting aneurysm. At necropsy, blood was found in one or the other pleural cavity in nine of our cases.

TABLE III. PRIMARY AND SECONDARY ANTE-MORTEM DIAGNOSES

PRIMARY		SECONDARY	
Cerebral accident	9		
Hypertensive heart disease	10	Hypertensive heart disease	4
Acute myocardial infarction	4	Coronary occlusion	4
Arteriosclerotic heart disease	2	Arteriosclerosis	3
Cardiac failure	3		
Dissecting aneurysm	9	Dissecting aneurysm	2
Embolism to femoral artery	1		
Bleeding ulcer	1	Bleeding duodenal ulcer	1
Uremia	2		
Pneumonia	1	Pneumonia	3
Carcinoma of esophagus	1		
Echinococcus cyst of liver	1		

Abdominal.—Symptoms referable to the gastrointestinal tract may occasionally be prominent. In 60 per cent of our cases in which pain was a symptom, the onset was with pain in the epigastrium. If the dissection has involved some of the gastric or mesenteric vessels, hematemesis or melena may lead one to suspect an intrinsic gastrointestinal lesion. Finklestein and Jacobi⁴¹ have emphasized that the only symptom in dissecting aneurysm may be abdominal pain simulating peptic ulcer. In a number of our cases, tentative diagnoses of bleeding ulcer or carcinoma of the esophagus or stomach had been considered. The presence of an abdominal mass may further obscure the picture. Reich⁶ found that 21 per cent of his cases had an abdominal tumor, and in one-half of these a diagnosis of abdominal malignancy was made.

Renal.—The last and least frequent syndrome is that in which renal symptoms are prominent. Rogers¹⁹ and Buckley⁴² have reported cases in which hematuria and back pain have been the outstanding symptoms. If this clinical picture is present, attention may then be directed toward the renal areas rather than the aorta.

CONCLUSIONS

1. The clinical and pathologic features of dissecting aneurysm are discussed.
2. Of the forty-four cases in the series we are reporting, eleven were diagnosed ante-mortem.
3. Sixty-seven per cent of the cases were in men, with the great majority occurring in the fifth and sixth decades.
4. Pain in the abdomen or chest is usually a prominent symptom, but no history of this was obtained in 55 per cent of our cases.
5. The sequence of events in the progress and radiation of the pain may be of diagnostic importance.
6. Dyspnea and neurological disturbances are other important symptoms.
7. The various physical findings are discussed. Emphasis is placed upon the diagnostic value of hemothorax, of the diastolic murmur of aortic regurgitation, and of the bizarre neurological findings.
8. The varied features presented by dissecting aneurysm of the aorta allow us to divide these cases into five syndromes; cardiovascular, pulmonary, cerebral, gastrointestinal, or renal.
9. An awareness of these syndromes, and a realization that any individual case may fall into one or all of these groups, should increase the frequency with which dissecting aneurysm is accurately diagnosed prior to necropsy.

The authors are extremely indebted to the medical chiefs and referring physicians of Philadelphia General Hospital and Jewish Hospital for permission to include their cases in this study.

ADDENDUM

The following are brief summaries of eleven of our forty-four cases which were diagnosed clinically.

CASE 4.—M. R., a physician 60 years of age, was admitted to the service of Dr. Mitchell Bernstein at Jewish Hospital on July 5, 1938, in a state of coma. The only history obtainable was the sudden development of unconsciousness. Examination revealed a temperature of 99° F., a pulse rate of 110, respirations of 40 per minute, and a blood pressure of 190/110. There was an obvious right hemiplegia and a systolic apical bruit. Death occurred in a few hours. Though the most likely diagnosis was that of hypertensive disease with a left cerebral thrombosis, the diagnosis of dissecting aneurysm was also made. This was confirmed at necropsy.

Diagnosis in this case depended upon a high degree of clinical suspicion. The suggestive findings were the sudden collapse, coma, and right hemiplegia. The average case with such a paucity of findings will probably escape recognition.

CASE 6.—D. M., 74 years of age, was admitted to the medical service of Dr. Harold Goldburgh, Jewish Hospital, on April 13, 1939. The patient had had mild effort angina and syncope for ten years. Two days prior to admission he experienced sudden severe bilateral lumbar pain. This was promptly followed by collapse. When admitted, the patient was pale and restless; the temperature was 101.3° F., the pulse rate, 120; respirations, 25 per minute; and blood pressure 90/60. There was a palpable mass in the left inguinal region, and a large ecchymosis over the left lumbar area. Leucocytosis, severe anemia, and elevation of the blood urea nitrogen were present. A number of red blood cells were found in the urine. The picture (proven at necropsy) seemed typical of ruptured dissecting aneurysm of the abdominal aorta.

Many of the classic signs are presented in this case. The severe lumbar pain followed by collapse, the elevated temperature, pulse, and respirations, the abdominal mass, the large left lumbar ecchymosis, and the hematuria were all typical of dissecting aneurysm.

CASE 8.—J. D., 58 years of age, was readmitted to the medical service of Dr. Harold Goldburgh at Jewish Hospital on November 26, 1940. He had been seen in the cardiac clinic for four years, and had experienced a severe myocardial infarction in 1939. While attending the cardiac clinic on the day of admission, he was seized with severe pain in the epigastrium. He broke into a profuse sweat and became dyspneic. On admission, the patient was obviously quite ill. Cyanosis, hypertension, cardiac enlargement, and cardiac failure were found. The femoral pulses were obviously unequal. Fever, tachycardia, tachypnea, and anemia developed. In view of his previous myocardial infarction, the diagnosis of acute myocardial infarction seemed likely. However, enough variations from the expected picture of myocardial infarction were present to support a tentative diagnosis of dissecting aneurysm. Death occurred four days after admission. At necropsy, inactive mitral rheumatic involvement was found, and a number of healed infarcts in the left ventricle. Death was due to a dissecting aneurysm which began in the abdominal aorta and involved both iliac arteries.

At first glance this was considered an acute myocardial infarction. However, the epigastric pain, the unequal femoral pulses, and the progressive anemia suggested an acute dissecting aneurysm.

CASE 9.—B. K., a 65-year-old physician, was admitted to the medical service of Dr. A. Margolies at Jewish Hospital on May 19, 1941. He had been a known hypertensive for a number of years and had previously recovered from a posterior myocardial infarction. In the summer of 1940, while on vacation, he experienced an attack of chest pain that was considered to be due to acute myocardial infarction, though the electrocardiograms did not confirm this diagnosis. When he returned to Philadelphia, orthodiagraphy revealed progressive increase in the size of the aorta. Hematemesis occurred, and a gastroenterologist who saw the patient felt that cirrhosis of the liver with esophageal varices was present. Dyspnea and cough increased, the hematemesis became more marked, and the aortic dilatation increased. Following a profuse hemorrhage, he was admitted to the hospital with a diagnosis of aneurysm of the aorta, with dissection and erosion into the esophagus. Death occurred in two days. Autopsy revealed a large dissecting aneurysm of the arch that had eroded into the esophagus, and two small saccular aneurysms of the thoracic aorta.

This case was diagnosed nine months before death. The progressive dilatation of the aorta following an episode of chest pain was demonstrated by orthodiagraphy. The erosion into the esophagus, cough, and hematemesis were valuable contributory findings.

CASE 15.—S. L., 53 years of age, was admitted to the medical wards of Philadelphia General Hospital on December 7, 1936. She had had two or three previous hemiplegias. The day prior to admission she experienced severe pain in the abdomen and back and, when admitted, was confused and semistuporous. Because of the confusion, the severe hypertension, the increase in temperature, pulse, and respiration, the elevated blood urea nitrogen, and the presence of red blood cells in the urine, a tentative diagnosis of dissecting aneurysm was made and confirmed at necropsy five days later.

The picture was fairly characteristic. The severe pain in the back and abdomen, mental confusion, increased temperature, pulse, and respiration rates, and hematuria were the diagnostic guide posts.

CASE 16.—J. H., 58 years of age, was admitted to Philadelphia General Hospital, service of Dr. Kalteyer, on June 23, 1937. Two days prior to admission he had experienced sudden severe epigastric pain that apparently did not respond to narcotics. It began to travel down the left side to the back and lower ribs. Dyspnea developed and became severe. On admission, the temperature was 100° F.; pulse rate, 120; respiration, 25 per minute; and the blood pressure, 132/98. Auricular fibrillation and a mitral systolic murmur were found. A pericardial friction rub was present, and the electrocardiogram was reported as diagnostic of pericarditis. Upon thoracentesis,

blood was obtained from the pleural and pericardial cavities. A diagnosis of dissecting aneurysm of the aorta with rupture into the pericardium was made by Dr. S. Bellet. The patient lived for five weeks; necropsy confirmed the clinical diagnosis.

The diagnosis here depended on severe migratory epigastric pain that did not respond to narcotics, a pericardial friction rub with an electrocardiogram diagnostic of pericarditis, and the aspiration of blood from the pleural and pericardial cavities.

CASE 19.—S. L., 46 years of age, was admitted to the service of Dr. H. Jump at Philadelphia General Hospital on May 12, 1940. He had had severe hypertension for many years. On the day of admission, he developed severe abdominal pain and vomiting. Dyspnea was also present. On admission, the temperature was 100° F.; pulse rate, 120; respiration, 25 per minute; and blood pressure, 270/130. The left leg was definitely cooler than the right. A leucocytosis of 13,000 increased to 53,000 in twenty-four hours. A diagnosis of dissecting aneurysm was made. At necropsy, the dissection was found to extend from the arch of the aorta down to the bifurcation, involving both renal arteries and partially obstructing the left iliac artery.

In this patient, the suggestive findings were the severe abdominal pain associated with dyspnea, the immediate increase in temperature, pulse, and respiration rates, the severe leucocytosis, and the marked decrease in the temperature of the left leg as compared to the right.

CASE 20.—H. F., 45 years of age, was admitted to the neurological service of Dr. A. Ornstein at Philadelphia General Hospital on July 8, 1940. On admission, the patient was confused and no adequate history could be obtained. Hypertension was present, and there was paralysis of the left leg and paresis of the left arm. A diagnosis of cerebral malacia due to dissecting aneurysm was made and confirmed at necropsy ten days after admission.

The diagnosis of dissecting aneurysm was made in this case because of the confusion and the atypical neurological findings.

CASE 21.—D. M., 52 years of age, was admitted to the medical service of Dr. D. Kramer, Philadelphia General Hospital, on May 17, 1940. On the day of admission he had suddenly become dizzy, experienced a choking sensation, and collapsed. He was semiconscious upon admission. Temperature, pulse, respiration, and blood pressure were all normal. The electrocardiogram suggested a possible posterior myocardial infarction. Because of the history and the presence of systolic and diastolic murmurs at the aortic area, a diagnosis of dissecting aneurysm of the aorta was considered. Death occurred in two days. The diagnosis was confirmed at necropsy.

Collapse and semiconsciousness together with the presence of systolic and diastolic murmurs at the aortic area were the basis for the diagnosis.

CASE 30.—M. D., 50 years of age, was admitted to Dr. D. Kramer's medical service at Philadelphia General Hospital on November 8, 1941. She had had hypertension for a number of years. For two weeks prior to admission she had complained of pain in the substernal area, cough, and dyspnea. The pain radiated to the shoulder blades. On admission, the temperature was 100° F.; pulse rate, 130; respirations 45 per minute; and blood pressure 300/180. There was flatness in the left chest; repeated thoracentesis always yielded bloody fluid. A systolic aortic murmur was heard, the murmur apparently continuously changing in character. Gradually the pain shifted from the interscapular area to the left chest and abdomen. None of the repeated electrocardiograms were diagnostic of myocardial infarction. The patient lived for two months, and at necropsy, the diagnosis of dissecting aneurysm with rupture into the pericardium and left pleural cavity was confirmed.

The important findings in this patient were the migrating chest and interscapular pain, the changing systolic murmur, and the recurrent left hemothorax.

CASE 40.—F. S., 57 years of age, was admitted to the medical service of Dr. S. Loewenberg, Philadelphia General Hospital, on November 7, 1945. His history prior to admission was interesting. He had had hypertension for years. Six months previous to admission there developed a gradual paresis of the left leg. This improved, but two months later he suddenly collapsed. His legs were unable to bear his weight. After a few days, their strength partially returned, but a cane was needed for support. On the day of admission, he suddenly collapsed, lost the use of

both legs, and complained of dyspnea. The temperature was 100° F.; pulse rate, 110 per minute; respirations, 36; and blood pressure, 270/130. The heart was enlarged and mild cardiac failure was present. The patient seemed to be slowly regaining the use of his legs, but death from respiratory failure occurred suddenly three days after admission. A diagnosis was made of thrombosis of the anterior spinal artery, possibly due to dissecting aneurysm. At necropsy, the dissection was found to extend to the renal artery on the left, with some involvement of the anterior spinal artery at that level.

The importance of the bizarre neurological changes as a basis for the diagnosis of dissecting aneurysm are well exemplified in this case.

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CHANGES IN THE CORONARY ARTERIES OF THE DOG FOLLOWING INJECTIONS OF ALLYLAMINE

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NECROSIS of the walls of arteries may occur as a part of general necrosis of tissue. It occurs more selectively in typhoid fever, typhus, tuberculosis, rheumatic fever, periarteritis nodosa, lupus erythematosus, serum sickness, and other conditions. Necrotizing arteritis is a prominent feature of malignant nephrosclerosis. The basic morphologic change in the arterial wall is fibrinoid necrosis of the media accompanied by more or less cellular exudate involving the vessel wall and often the periadventitial tissues. This exudate may vary in the type of constituent cell. Thrombi may complicate the picture.

Changes of a similar character have been produced in the experimental animal by several procedures. These include, among others, renal ischemia in dogs,^{1,2} sensitization of rabbits by the injection of horse serum,³ and unilateral nephrectomy in rats combined with injections of desoxycorticosterone.⁴ Subcutaneous injections of trypsin,⁵ besides digesting tissues locally, has led to segmental necrosis of artery walls.

The necrotizing vascular lesions which follow bilateral renal artery ligation in the dog seem to be associated in part with the presence within the body of ischemic kidney tissue.⁶ With this fact in mind, the literature was searched to see if any derivative of tissue breakdown was known to result in such lesions when injected into animals. The report of Mellon and associates⁷ was of particular interest. These investigators reported the production of acute arterial lesions locally in rabbits that had been injected intradermally with low concentrations of a buffered unsaturated aliphatic amine, allylamine: $\text{CH}_2 = \text{CH} - \text{CH}_2 - \text{NH}_2$.

Mellon and associates had become interested in this substance through the work of Eppinger and co-workers.⁸ Eppinger had identified allylamine as a toxic substance in the tissues of animals dying of experimental paratyphoid infections, and had shown that pure solutions injected intravenously caused great increase in capillary permeability and marked edema of blood vessel walls,

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of the heart valves, and of the gastric and duodenal mucosa. These observations seemed to warrant further investigation.

The work herein reported presents the results of injections of allylamine and of related substances intravenously in dogs together with the results of a few intrapericardial injections of the same materials.

METHODS

Allylamine is a strong base. For injection it was prepared as a 1 per cent aqueous solution neutralized with hydrochloric acid and buffered to pH 7.4. Fifteen milligrams per kilogram of body weight of the base were injected initially. At this level, severe immediate reactions were avoided. N-propyl amine, used as a control for the allylamine, was prepared in the same way and was injected in the same doses. Allyl alcohol and other nonbasic homologs were injected as 1 per cent aqueous solutions at pH 7.4, at the same dosage levels.

The intrapericardial injections were made under direct vision through a chest incision, utilizing nembutal anesthesia and positive pressure respiration. Ten cubic centimeters of the sterile buffered solution was placed in the pericardial sac through a small needle.

Following an intravenous injection of 15 mg. per kilogram of allylamine, there is no immediate reaction. Within a few minutes the dog usually becomes restless and may vomit and defecate. These signs continue for some minutes, then disappear. The majority of dogs survive 20 mg. per kilogram as an initial dose, but may become wildly excited for fifteen or twenty minutes. With this dose some die within twelve to twenty-four hours. With higher doses severe reactions are common and within a few hours the animals become prostrated with a falling blood pressure and a remarkably increased hematocrit. Death occurs in stupor. In dogs, even lethal doses have no immediate effect on the systemic blood pressure. In rabbits, very large doses of the amine injected intravenously lead to marked pupillary constriction after some minutes.

The majority of dogs in the present experiment were given two or more doses of the amine, as it was found that the changes occurring in the cardiovascular system increased and became progressive with repeated injections. The usual procedure was to give an initial dose of 15 mg. per kilogram and to follow it with a similar dose twenty-four to forty-eight hours later. Further injections might be given at intervals of two or three days, depending on the condition of the animal and the purpose of the experiment. It was found after the first few injections that most dogs would tolerate injections of 20 mg. per kilogram every three to five days. In the chronic experiments the animals were watched carefully and were rested, if necessary, at any stage before continuing injections. In spite of these precautions unexpected deaths in the series have occurred.

Although some acute changes in the cardiovascular system were observed in animals dying in the first twenty-four hours following a single injection of allylamine, these changes were best seen in animals three or four days after the last of two or three injections given as indicated. More chronic, progressive

changes, as well as acute lesions, have been found in animals surviving longer periods and given repeated doses.

In all, the tissues of about fifty dogs have been examined. The formalin fixed sections have been stained with Masson's trichrome method, hematoxylin and eosin, Weigert's elastic tissue stain, and Sudan IV.

RESULTS

The changes following intravenous injections of allylamine involve particularly the medium-sized and smaller muscular coronary arteries, the arteries of the retroperitoneal mesenteric fat, the peripheral body fat itself, and, to a lesser extent, the myocardium, the kidneys, and the liver.

Changes Following a Single Lethal Dose.—In animals dying six to twenty-four hours after a lethal dose, there is little to be seen grossly or microscopically except for large zones of extravasated fluid in the retroperitoneal and epicardial fat. Occasionally, massive hemorrhages may be found in these regions as well. While the majority of the blood vessels at this interval are not strikingly altered, a few in the epicardial fat have clear, swollen medial cells, and an occasional epicardial vessel with a fused, fuchsinophilic, edematous media has been observed. Accompanying cellular exudate has been present. There may be cloudy swelling and interstitial edema of the liver and kidneys. These changes have been noted at this interval only after large, rapidly fatal, intravenous injections.

Acute Changes Following Repeated Intravenous Injections.—Survival for three to four days after two or three injections of allylamine, 15 mg. per kilogram, is associated with striking changes in the blood vessels and adipose tissue. Grossly, there are petechial and confluent hemorrhages in the epicardial fat. The fat itself is indurated and discolored. Similar changes are present in the mesentery.

Microscopically, the medium-sized and smaller muscular coronary arteries, both superficial and penetrating branches, are the seat of an intense acute necrotizing process (Figs. 1 and 3). Many vessels are involved, the changes varying in stage and intensity. Segments of the medial smooth muscle are fused into amorphous, brightly acidophilic masses. Numbers of extravasated red blood cells may be present in the media or adventitia, or both. Polymorphonuclear leucocytes and large mononuclear cells may be present in the necrotic media and in the surrounding adventitia, but they may be few in number or be entirely absent. The perivascular exudate may be composed solely of mononuclear cells. No eosinophilic leucocytes have been encountered in the lesions studied. While the internal elastic membrane usually remains intact, it may be thin, swollen, or frayed. There is very little other elastic tissue in vessels of this size in the dog's heart. In vessels in which the medial changes are more advanced, no remnant of the smooth muscle fibers can be identified. The medial segment appears shrunken and is composed of a homogeneous ground substance that takes a light green stain with Masson's method.

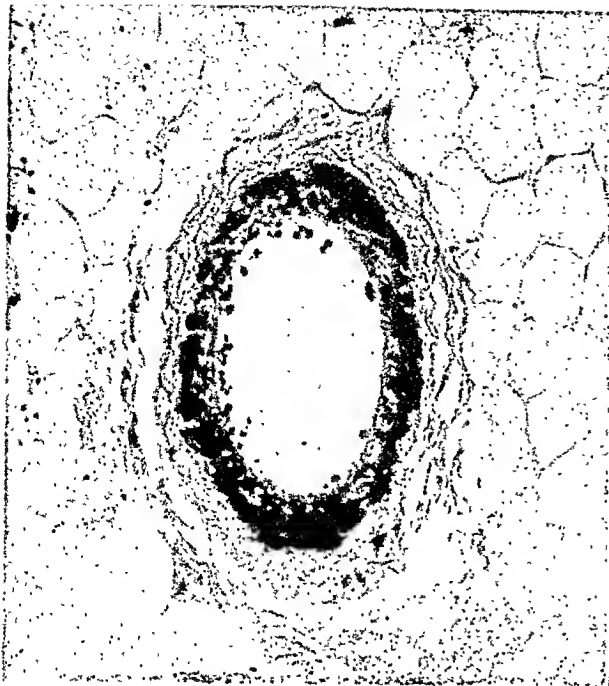


Fig. 1.

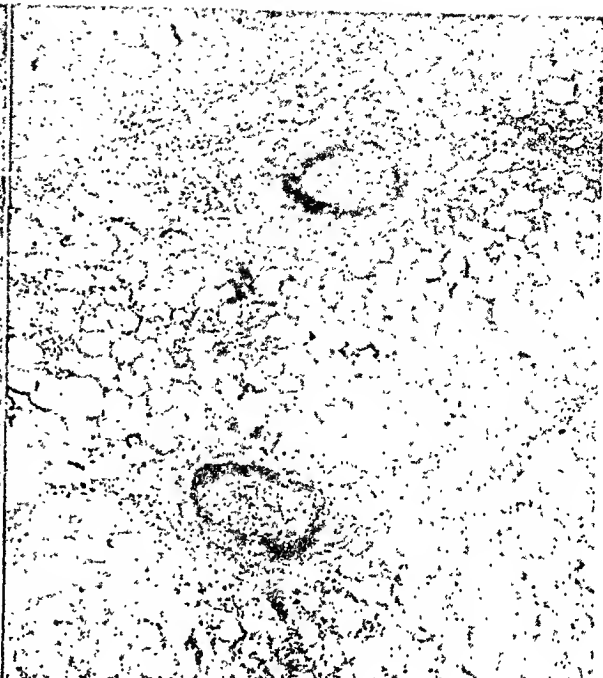


Fig. 2.

Fig. 1.—Dog. Coronary artery four days after two intravenous injections of allylamine. Fibrinoid necrosis of media. Lack of periadventitial and adventitial inflammation. $\times 105$.

Fig. 2.—Dog. Arterioles in mesenteric fat four days after three intravenous injections of allylamine. Acute necrotizing arteritis. Perivascular cellular exudate. Hemorrhage and exudate in fat. $\times 75$.

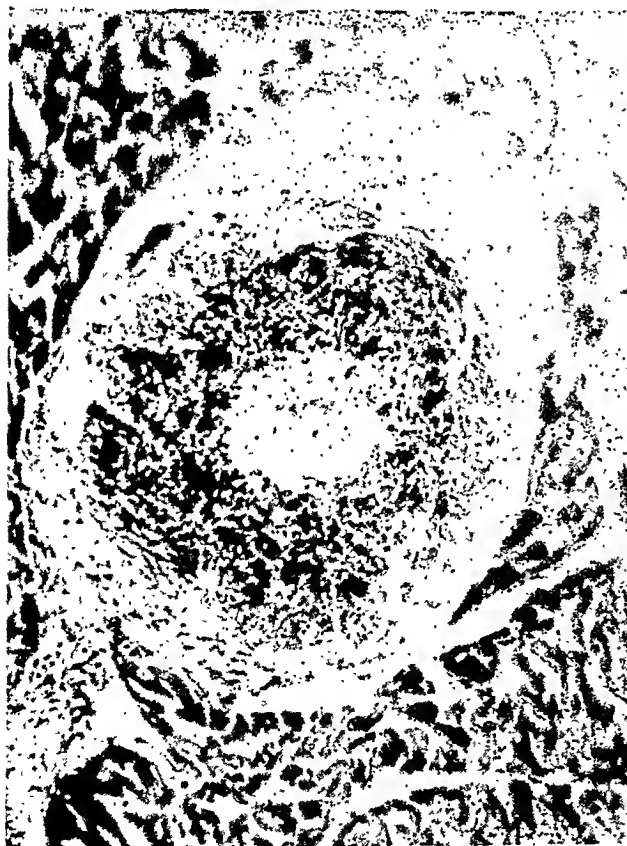


Fig. 3.

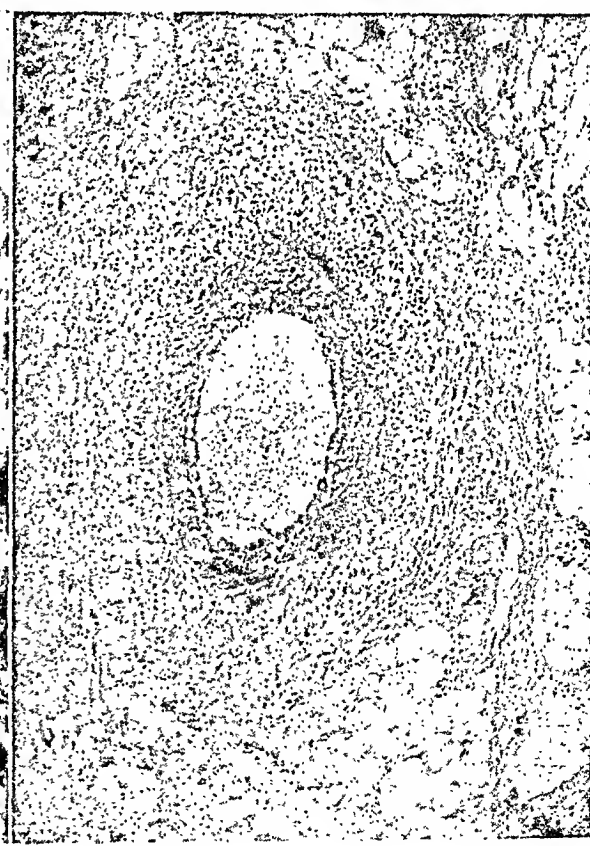


Fig. 4.

Fig. 3.—Dog. Coronary artery, penetrating branch, of left ventricle four days after two intravenous injections of allylamine. Periadventitial cellular exudate. Fibrinoid necrosis of and hemorrhage in media. $\times 80$.

Fig. 4.—Dog. Coronary artery four days after two intravenous injections of allylamine. Periarthritis. Small area of fibrinoid necrosis of media. Elevation of endothelium. $\times 120$.

The intima of the muscular coronary arteries of the dog consists of the endothelium lying directly on the internal elastic membrane. In severely damaged vessels, a segment or the whole circumference of this endothelium is raised from the underlying elastic membrane and fluid and mononuclear cells appear in the thus created subendothelial space (Figs. 4 and 5). Thrombi have only occasionally been observed in the lumina of the involved coronary vessels. The detached endothelium with its underlying fluid and cells may extend far into the lumen of the vessel.

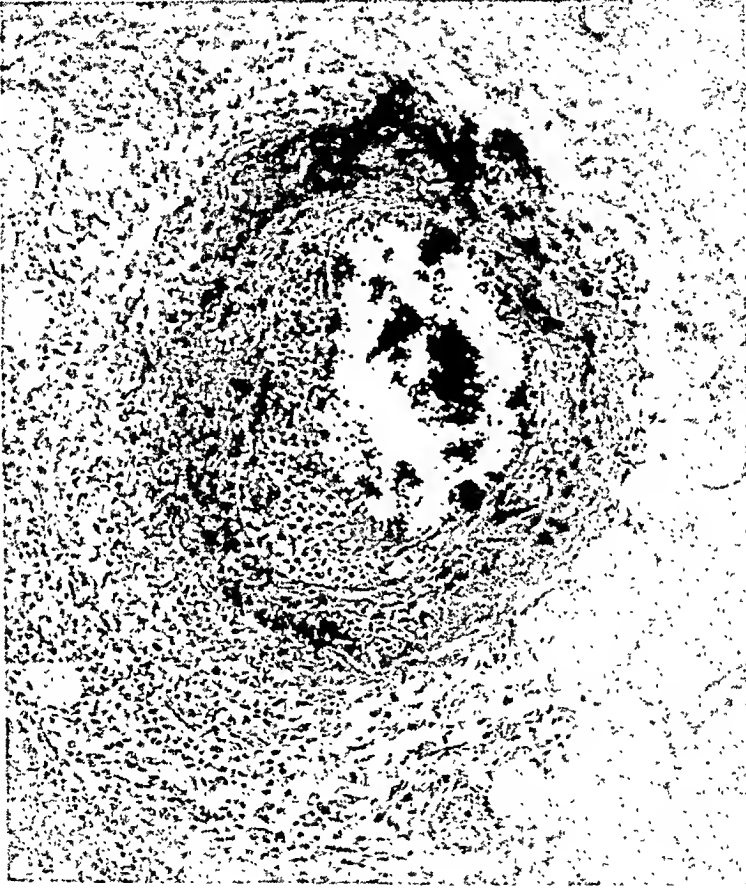


Fig. 5.—Dog. Coronary artery five days after three intravenous injections of allylamine. Intense periarterial exudate. Fibrinoid necrosis of media. Elevation of endothelium. Subendothelial space filled by a mosaic of large clear mononuclear cells. Erythrocytes in reduced lumen. $\times 200$.

Hemorrhage into the vessel walls, even in the smallest arteries, is prominent and appears to arise from the vasa vasorum in the adventitia and outer media. The red blood cells may be found throughout the media and even in the subendothelial space formed by the elevation of the endothelium.

Acute alterations in the mesenteric arterioles and in fat elsewhere in the retroperitoneal region are similar to those in the coronary arterioles, although the number of vessels involved is usually less (Fig. 2). No vascular changes of a similar nature have been seen after allylamine injections in the kidneys, liver, gastrointestinal tract, or other viscera.

Extravasated fluid in the depot fat has been described as an early finding after large single injections of allylamine. This exudate is seen in animals also after smaller repeated doses devised to allow longer survival. In these dogs there is precipitation of a fibrillar substance, probably fibrin, in the fluid as well, and there may be focal or diffuse cellular reaction. Necrosis of fat is not prominent, but probably occurs. Focal hemorrhages are numerous. Vessel changes in the epicardial fat seem to develop simultaneously with those in the fat itself. Very early many of the capillaries appear to contain hyaline thrombi, but it is difficult to ascertain whether or not the changed appearance of these vessels is due to a luminal mass or to an altered condition of the wall.

Cloudy swelling and interstitial edema may be present in the kidney and liver. There may be, in some animals, fatty change in the renal tubules. In no instance has this led to nitrogen retention. Small, focal myocardial necroses are present in many animals. Occasionally, these are extensive.

Changes in Animals Repeatedly Injected and Allowed to Survive Six Weeks or Longer.—In animals repeatedly injected and allowed to survive a longer period of time, a progression of the changes already described occurs. Additional coronary vessels of the same caliber are involved in the acute necrotizing process. The medial coats of those involved early are now composed entirely of fibrous connective tissue. Fresh hemorrhages may be present, however, in the altered media. In many vessels striking changes have occurred in the intima. The undifferentiated mononuclear cells that accumulate beneath the endothelium are transformed into masses of connective tissue with newly formed blood vessels.

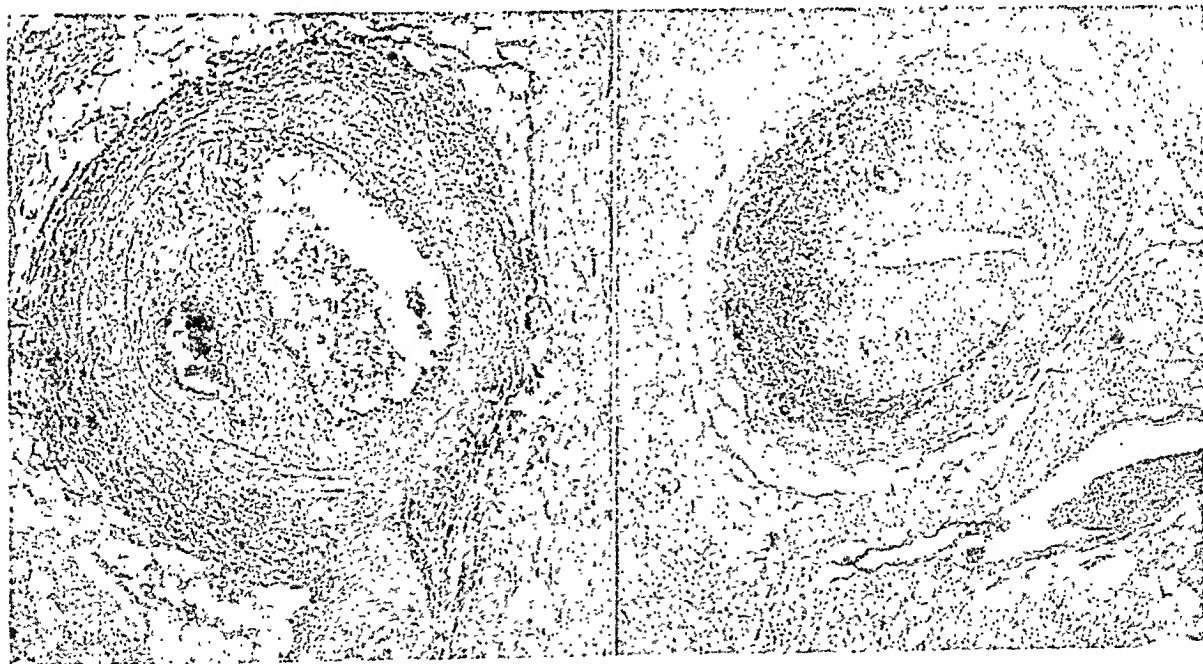


Fig. 6.

Fig. 7.

Fig. 6.—Dog. Coronary artery after six weeks of a course of twelve intravenous injections of allylamine. No acute inflammatory changes. Fibrosis of media. Fibrous proliferation of intima with reduction of lumen and a new vascular channel. Note the internal elastic membrane. $\times 320$.

Fig. 7.—Dog. Coronary artery after six weeks of a course of fifteen intravenous injections of allylamine. Thin fibrous media. Massive intimal proliferation with new blood vessel formation. Hemorrhage in media and intima. Original lumen of vessel reduced to a central slit. $\times 140$.

This granulomatous endarteritic process may seriously encroach on the lumina of the vessels. Thrombi are usually not present. There may be massive hemorrhages into the thickened, intimal tissue. Fat stains of such vessels so far have revealed lipoidal substances only in areas of hemorrhage. Twelve to fifteen injections over a period of six weeks resulted in the changes described (Figs. 6 and 7). Lesions were not equally developed in every animal. There is a large individual variation.

Chronic changes in the body fat consist in a progressive fibrosis with some giant cell reaction. Hemorrhagic areas become organized. A few arterioles may be found with greatly thickened fibrous walls, and reduced lumina.

Fatty livers have been observed regularly in dogs kept on allylamine injections for six weeks or longer. In this connection it should be mentioned that unless rest periods are given, the dogs eat very little and lose weight rapidly. If the drug is discontinued, they resume eating and appear normal.

Changes Following Intrapericardial Injections of Allylamine.—In order to see if the coronary arteries would be injured locally by allylamine, 10 c.c. of the neutralized 1 per cent solution was injected directly into the pericardial sacs of a series of normal dogs (Figs. 8, 9, and 10). After twenty-four hours, there were gross hemorrhages and induration of the epicardial fat. Dogs examined after four days revealed the most extensive necrotizing and endarteritic changes in the muscular coronary arteries. These changes are qualitatively like those following intravenous injection. Invariably, however, the segment of the vessel nearest the epicardial surface was most intensely involved. The fibrinoid change tended to occur first in the outer layers of the media, and there was much more periarterial cellular exudate.

The arterioles of the parietal pericardium are also involved. There is a mild fibrinous pericarditis, with changes in the subepicardial fat similar to those occurring after intravenous injection. No lesions were found elsewhere in the body. The more chronic changes occurring in the coronary vessels following repeated intrapericardial injections of allylamine are being investigated.

Changes Following Bilateral Nephrectomy and Injections of Allylamine.—Acute necrotizing arteritis of the coronary arteries and of the arterioles of the mesenteric fat were found in three bilaterally nephrectomized dogs injected with allylamine.

Control Groups.—Control groups of dogs have been given intravenous injections of n-propyl amine, allyl alcohol, allyl formate, allyl thiourea, and allyl chloride according to the same dosage plan and in equal gram-per-kilogram doses. N-propyl amine and allyl alcohol have been injected intrapericardially. The animals have been studied three to four days after the last injection. Comparable vascular lesions have not been found. One necrotic arteriole in the liver of a dog receiving allyl formate intravenously was observed. This liver was the seat of widespread parenchymatous necrosis. Edema of the submucosal gastric vessels, but no necrosis, was observed after intravenous injections of allyl alcohol. These vascular changes formed part of the massive hemorrhagic edema of the stomach

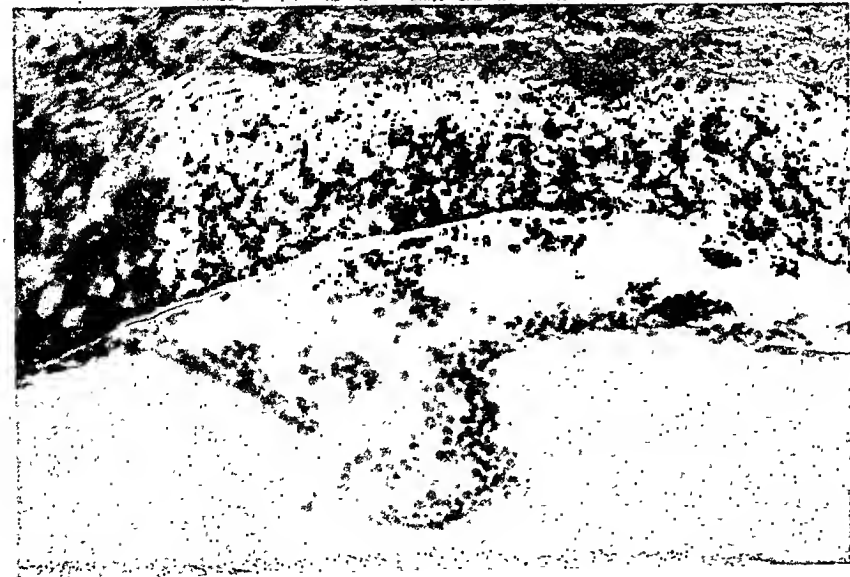


Fig. 8.

Fig. 8.—Dog. Inner portion of wall of large coronary artery five days after injection of allylamine intrapericardially. Edema and fibrinoid necrosis of medial cells. Cellular exudate in necrotic media. Elevation of endothelium with masses of small mononuclear cells in the subendothelial space (these are not red blood cells). $\times 45$.

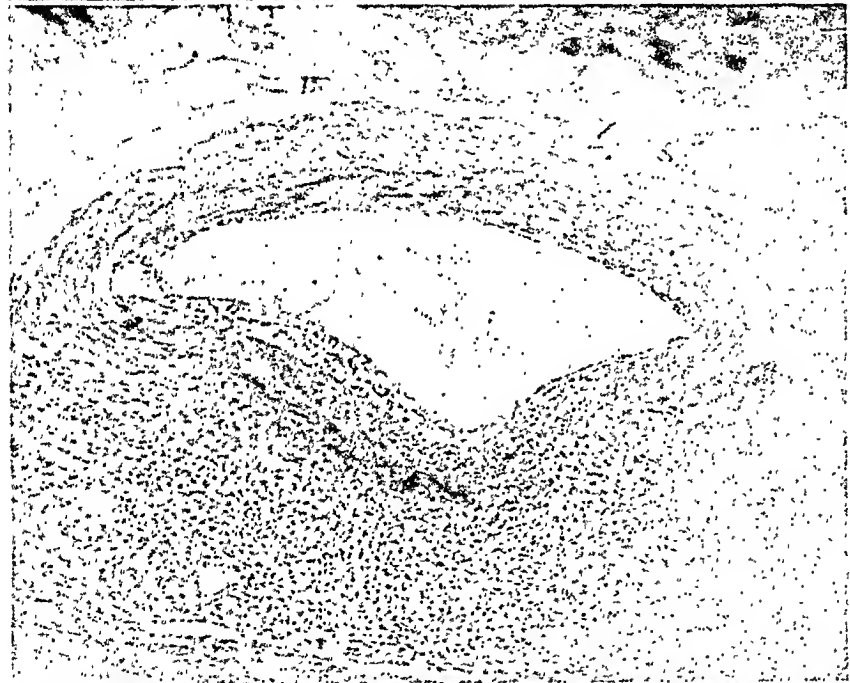


Fig. 9.

Fig. 9.—Dog. Coronary artery five days after one injection of allylamine intrapericardially. Segmental perivascular inflammatory reaction. Advanced medial necrosis. Elevation of endothelium with subendothelial mononuclear exudate.



Fig. 10.

Fig. 10.—Dog. Another coronary artery from same animal as Fig. 9. Sharp segmental localization of mural changes. Subendothelial exudate. Lumen reduced nearly one-half.

that was regularly observed following intravenous injections of allyl alcohol. This lesion, first described by Eppinger, will be the subject of a subsequent report.

Injections of allylamine into a few rabbits and rats has led to the preliminary conclusion that these species do not regularly develop, at these dose levels, the vascular lesions described. Changes in the body fat similar to those in the dog have been observed.

DISCUSSION

Injection of allylamine in dogs affords a relatively simple, concrete starting point for a study of the pathogenesis and fate of arterial lesions that are basically like those occurring in certain diseases of man. Time and further experimentation will be required to evaluate the effect of the progressive changes in the coronary arteries on the total physiology of the heart. Much further experimentation, some of which is now in progress, will be needed to ascertain what role, if any, volatile unsaturated amines or related substances play in the etiology and pathogenesis of diseases in man or in the experimental animal. Finally, in allylamine, a tool is provided for the investigation of the relationship, if any, of acute vascular disease to the more common chronic forms of disease of the arterial wall.

SUMMARY

Preliminary report of the pathologic changes occurring in dogs after single and repeated injections of allylamine and related substances has been made. The progressive morphologic changes occurring in the coronary arteries and in the body fat have been described in some detail. The similarity of the vascular lesions to those occurring in certain diseases of man has been pointed out and plans for further study indicated.

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THE EFFECT OF LOCAL COMPRESSION UPON BLOOD FLOW IN THE EXTREMITIES OF MAN

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THE question as to whether the circulation in the limbs is significantly reduced by the application of moderate local pressure is of interest not only to specialists in peripheral vascular disease, but also to surgeons, orthopedists, and others concerned with the application of constricting apparatus on the limbs. This is because of the recent recognition of the fact that warmth and health of the extremities depend directly upon the adequacy of their circulation, and only indirectly upon the abundance of insulation around them. A great deal of attention, therefore, has been paid by the Armed Services, for example, to the circulatory effects of constricting clothes, gloves, and shoes,¹ especially in cold environments where they have been found to be of importance in the incidence of frostbite and of immersion or trench foot.

Previous studies in this laboratory² have demonstrated a reduction in blood flow to the extremities during elevations of venous pressure produced by inflating pneumatic cuffs on the proximal portion of the limbs. The present study was undertaken to determine the effects of mild to moderate external compression, uniformly applied to different parts of normal extremities, upon the local blood flow. Three methods previously found valid for estimating blood flow in the extremities under such conditions were used: (1) thermometric, (2) blood gasometric, and (3) plethysmographic.

METHODS AND RESULTS

Thermometric Method.—The temperature of the skin provides an index of circulatory changes in the skin when the environmental temperature is maintained at a relatively constant level, lower than body temperature. Such measurements are simple and easy to make, but have the disadvantages of being difficult to quantitate in terms of volume of blood flow, and of having too much lag to allow the detection of fleeting circulatory changes.

In the present experiments, copper-constantan thermocouples were attached to at least two corresponding finger pads of each hand. The hands were

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sealed in airtight plethysmographs,³ out of which the thermocouple wires were led to a galvanometer through a selector switch. A centigrade mercury thermometer was inserted into each plethysmograph for the measurement of air temperature within the apparatus. Every three to five minutes, galvanometer readings were made, accurate to 0.1° C., measuring the temperatures of the several finger pads in rapid succession; the plethysmograph temperatures were also recorded.

The subjects lay in an air-conditioned room, and were comfortably warmed with blankets and heating pads so as to produce mild peripheral vasodilatation. After a control period of ten to twenty minutes the air pressure within one of the plethysmographs was increased to 20 or 30 mm. Hg above atmospheric by connecting it through a valve to a large bottle containing air at the desired pressure. The opposite plethysmograph was kept at atmospheric pressure for control observations. After ten to sixty minutes of pressure, the plethysmograph was deflated and another period was allowed for control conditions to be resumed. Then, either the same hand was exposed to a different pressure, or was utilized as the control while pressure was applied to the opposite hand.

The results of a typical experiment are illustrated in Fig. 1. The temperatures of the fourth finger of the right hand (RF_4) and of the corresponding finger of the left hand (LF_4) are graphed during the application and removal of the indicated pressures. In addition to the changes in skin temperature produced by local pressure, there occurred spontaneous variations due to vasomotor activity in the fingers which tended to be similar on the two sides. In order to lessen the confusion introduced by these spontaneous changes, the *difference* in temperature between the right and left fourth fingers is plotted at the bottom of the figure, with increasing positive values denoting an increase in the temperature of the right side relative to that of the left. The graph shows that when 20 mm. Hg pressure was applied to the right hand, no clear-cut effect was observed except for similar spontaneous fluctuations on both sides. The same pressure applied to the left hand caused the temperature on that side to drop perceptibly, thus producing a rise of the difference curve. The subsequent application of 30 mm. Hg pressure on each side, in turn, was followed by a rather large decrease in relative temperature of that respective side.

Similar tests were carried out on five subjects, all with normal peripheral circulation. Uniformly, when positive pressure on the hands produced any effect, it caused a decrease in skin temperature as compared with that of the opposite control limb. A summary of the data is presented in Fig. 2. In each test, the temperatures were averaged for the periods before, during, and after each application of pressure, beginning five minutes after each change. The resulting figures from all the tests were then averaged and plotted in the graph. These mean values show that a local pressure as small as 20 mm. Hg produced a definite reduction in skin temperature, while one of 30 mm. Hg resulted in a greater reduction, averaging about 1° centigrade. The mean decrease in skin temperature is shown in relation to local pressure in Fig. 3.

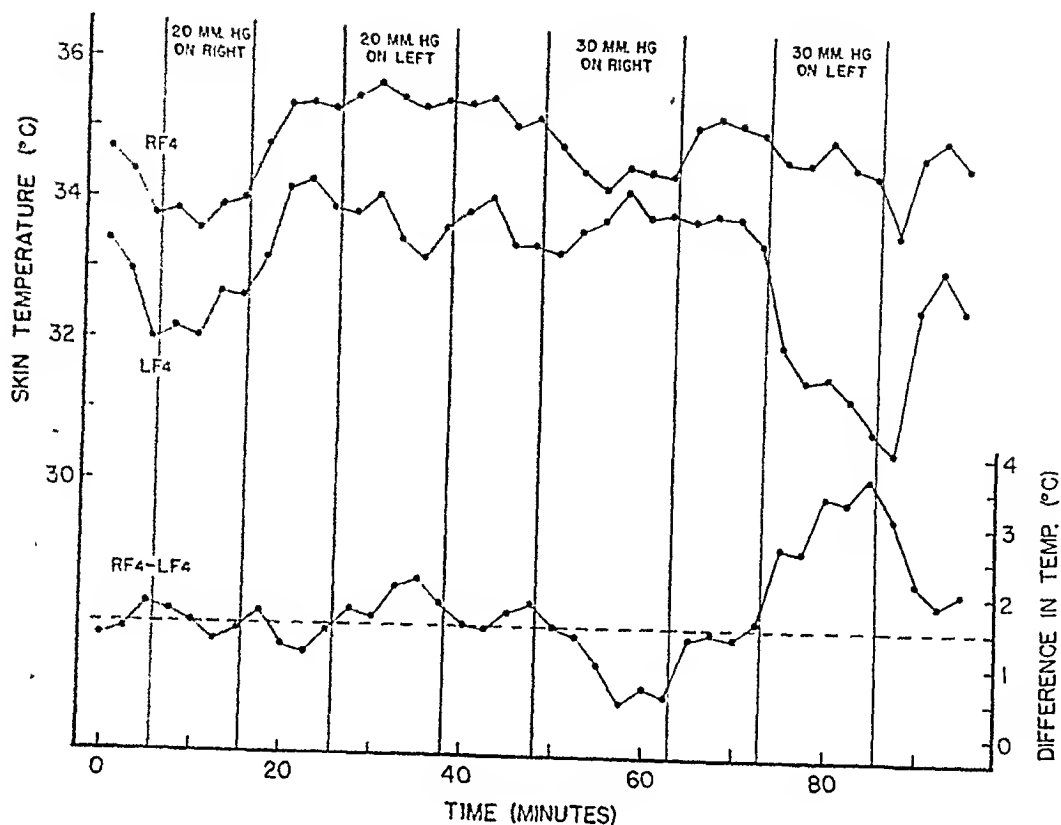


Fig. 1.—Typical experiment on the effects of local pressures of 20 and 30 mm. Hg on the skin temperature of the tips of the fourth finger of the right hand (RF₄) and left hand (LF₄). The lowest curve, showing the difference in temperature between RF₄ and LF₄, is presented in order to lessen the confusion introduced by spontaneous vasomotor changes. The broken horizontal line denotes the mean value of the temperature difference in the absence of pressure.

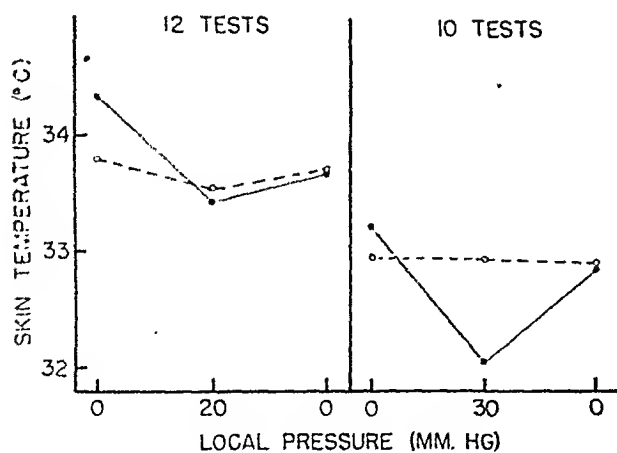


Fig. 2.

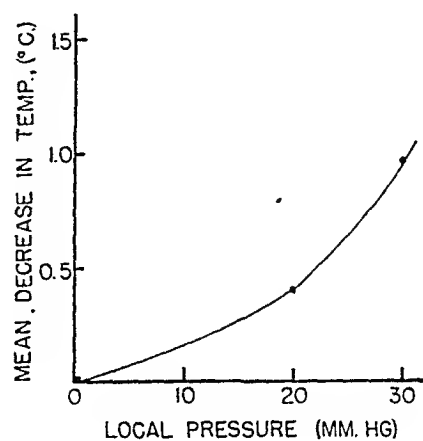


Fig. 3.

Fig. 2.—The mean effect of local pressure on the temperature of the fingertips. The average temperatures are indicated before, during, and after application of pressure. The solid lines represent the experimental hand, and the broken lines represent the opposite (control) hand.

Fig. 3.—The relation between local pressure and the mean decrease in the temperature of the fingertips in the experiments shown in Fig. 2.

Skin temperature measurements during the application of a pressure of 50 mm. Hg were carried out on two subjects. The mean decrease in finger tip temperature was 2.5° centigrade. During this time, moreover, the subjects were warmed so that the mean temperature of the control hand increased 2.3° centigrade. The effect of local compression of 50 mm. Hg, therefore, was a temperature reduction of 4.8° C. on the experimental as compared with the control side.

Blood Gasometric Method.—The blood flow through an organ may be determined, according to the Fick principle, by dividing its oxygen uptake by the arteriovenous oxygen difference. The rate of oxygen uptake by a given forearm under resting conditions has been shown to be fairly constant.⁴ Likewise, the arterial oxygen content normally remains fairly constant. Changes in the blood flow through a resting forearm may therefore be estimated by determining the alterations in the venous oxygen content. If the blood flow decreases, more oxygen is extracted from a given volume of blood during its passage through the tissues and the venous oxygen content falls.

This method was applied to the present problem as follows. Blood was obtained from the antecubital veins of both arms before, during, and after compression of one forearm, the opposite arm serving as a control. In order to avoid repeated venipunctures, with concomitant reflex disturbances in circulation, indwelling needles with obturators (Unger type, gauge 18) were employed. Before each experiment these were inserted pointing distally into the veins through the skin, previously infiltrated with 1 per cent procaine hydrochloride. Blood samples could be taken, when desired, simply by removing the occluding stylets from the needles and attaching oiled syringes, containing sufficient heparin solution to fill the dead space in the tip. The blood samples were handled anaerobically and stored over mercury in a refrigerator. Each sample was analyzed in duplicate for content of "oxygen" by the technique of Van Slyke and Neill.⁵ The allowable difference of duplicate analyses was 0.10 volume per cent. The arterial oxygen content was estimated from the oxygen capacity of the venous blood, assuming an arterial oxygen saturation of 96 per cent. Hematocrit determinations in duplicate were also made on each sample by the method of Wintrobe.⁶

Experiments were first done by a procedure (designated as *Method I*) which, as will be shown, proved to be unsatisfactory. Another group of experiments (designated as *Method II*) was performed by an improved technique. Finally, a series of *control* experiments was carried out in which no pressure was applied to either side.

Method I: These experiments were carried out according to the following procedure. The needles were inserted as described and pneumatic cuffs were applied snugly but without pressure, covering each forearm up to about 2 cm. below the tips of the needles. The hand circulation was occluded at the start of each experiment by inflating separate cuffs on the wrists at a pressure greater than systolic. After four to five minutes the first pair of blood samples was

taken. One forearm was then subjected to the desired pressure (20 or 30 mm. Hg) by inflating the cuffs. After four to five minutes a second pair of samples was obtained. The pressure on the forearm was then discontinued and a third pair of samples obtained after another four to five minute interval. Finally, the wrist cuffs were deflated.

The results of these earlier tests are summarized in Fig. 4. Graph A represents the mean of ten experiments in which a pressure of 20 mm. Hg was applied to one forearm (solid curve). During compression, the venous oxygen content decreased about 1 volume per cent. The mean arteriovenous oxygen difference thus rose from 6.4 to 7.4 volumes per cent, an increase of 15 per cent. The calculated blood flow correspondingly decreased 15 per cent. The averages for the opposite arm, which served as a control (broken curve) showed no significant change in venous oxygen content. With 30 mm. Hg pressure (Graph B), the mean decrease in venous oxygen content was somewhat greater, corresponding to a 20 per cent decline in calculated blood flow. The control arm showed a much smaller mean change, in the opposite direction.

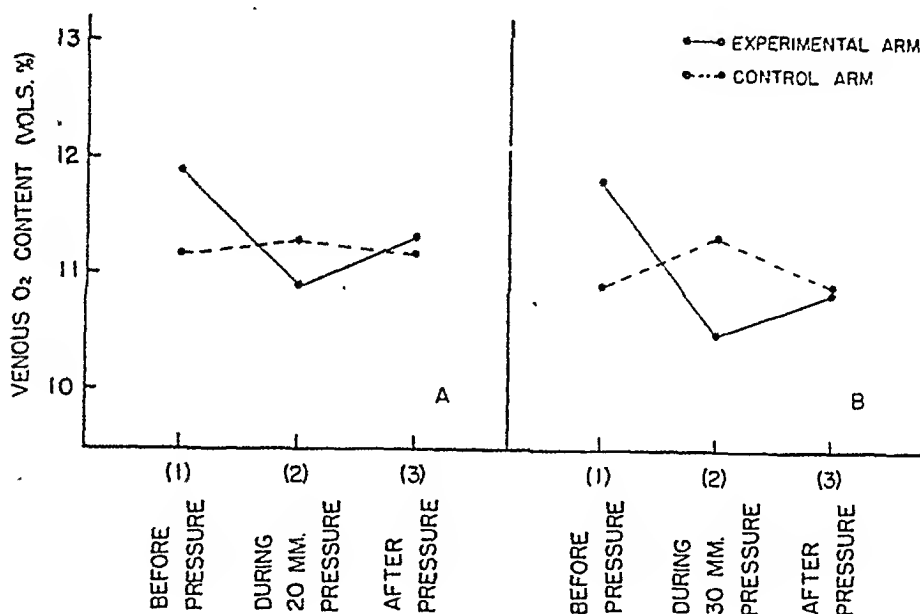


Fig. 4.—The mean results of the blood gasometric experiments performed by Method I. For reasons explained in the text, this method of sampling venous blood proved unsatisfactory during the application of pressure.

A. Mean oxygen content of venous blood from the arm during application and removal of 20 mm. Hg pressure. The average arterial oxygen content of this group of ten subjects was 18.3 vols. per cent.

B. Similar data for experiments with 30 mm. Hg pressure. The average arterial oxygen content of this group of six subjects was 19.6 vols. per cent.

A statistical analysis of the significance of the changes in oxygen content in these experiments was made by the method of Fisher.⁷ It was found that the mean decrease in venous oxygen content on applying 20 mm. Hg pressure was barely significant ($P^* = 0.04$), while that on applying 30 mm. Hg pressure just

* P represents the probability that the observed change may occur by chance. Values of 0.05 or less indicate statistically "significant" changes, and those of 0.01 or less indicate "highly significant" changes.

lacked statistical significance ($P = 0.06$). The recovery on releasing the pressure in both groups lacked significance (P values were 0.16 and 0.62, respectively). The spontaneous changes in the control arm were not significant (P values between 0.40 and 0.97). The relatively poor statistical significance of the experimental data obtained by Method I is attributable to the following observations.

Although local compression of the forearm caused a definite reduction in the oxygen content of the venous blood samples in most of the experiments with Method I, in others there was only a slight, or occasionally even a reversed, effect. Such aberrant results were obtained even when the venous blood flow, as judged by the ease of securing blood from the vein, was definitely decreased; in fact, the erratic results were most marked in just those instances when the blood was most difficult to obtain. This consideration caused doubt that the samples truly represented the venous blood issuing from the compressed area, but rather consisted of a mixture of such blood with that refluxing in the vein from above the compressed area. In order to obviate the possibility of such a mixing, the technique of sampling was changed in the subsequent experiments.

Method II: In the later tests, the Unger needles were inserted as before. However, a flexible venous catheter, stiff enough to withstand the compression of the cuffs, was attached to the needle on the arm to be compressed. The cuffs were applied and extended from the distal part of the forearm to the middle of the upper arm, covering the needle as well as the catheter leading upward from it. By sampling the venous blood from a site near the middle of the compressed area instead of at its proximal border, one might expect that the reflux of blood from noncompressed areas would be prevented. A constant slow drip of isotonic saline solution was instilled through the catheter and needle to keep them patent. At frequent intervals, measurements of venous pressure were made through this system by the technique of Moritz and von Tabora.⁸ On the control side, the same sampling technique was used as in Method I. Samples were obtained by the same procedure as in the earlier experiments except that the initial 5 c.c. from the catheter were discarded to clear the system of saline solution.

The individual results of the experiments carried out with 30 mm. Hg pressure by the improved technique (Method II) are shown in Table I* and the mean results in Fig. 5 (left). The results obtained by this method *uniformly* showed that the venous oxygen content was decreased during compression. The mean arteriovenous oxygen difference rose from 6.8 to 9.1 volumes per cent, signifying a 25 per cent decrease in blood flow. On removal of the pressure, the oxygen content rose almost to its initial value. Statistically, these changes were highly significant, the P values being less than 0.01. The changes in the control arm were not significant, the P values when the pressure was applied and removed being 0.72 and 0.26, respectively.

*The hematocrit values of samples obtained through the catheter often were not identical with those obtained from the opposite arm, probably due to slight dilution by the saline solution. However, the difference between the hematocrit determinations on corresponding samples rarely exceeded 0.5 per cent. In case of a difference, the oxygen content of the experimental sample was corrected by the factor necessary to equalize the hematocrits. The tables present the corrected oxygen contents.

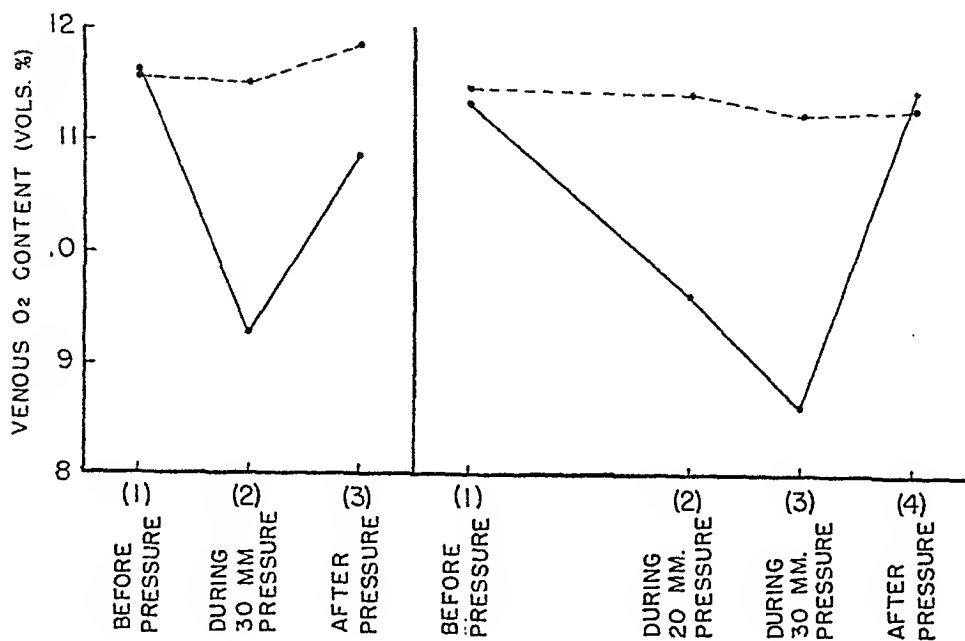


Fig. 5.—The results of the blood gasometric experiments performed by Method II. Each graph shows the mean data of five experiments (see Tables I and II for individual figures). The solid lines represent the arm on which the pressure was applied; the broken lines, the opposite control arm. The mean arterial oxygen contents of the two groups of subjects were 18.4 and 16.6 vols. per cent, respectively.

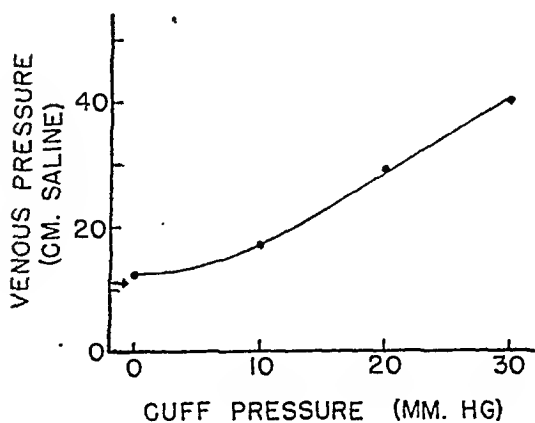


Fig. 6.

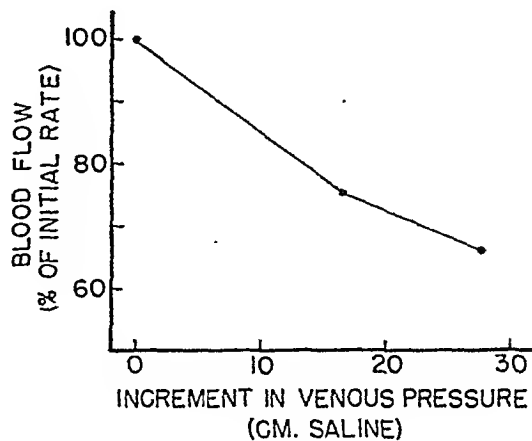


Fig. 7.

Fig. 6.—The relation between the pressure in the pneumatic cuffs on the forearm and the mean venous pressure beneath the cuffs. The venous pressures refer to the level of the needle in the vein as zero. The arrow represents the mean level of the sternum. Since 1 mm. Hg pressure is equivalent to about 1.34 cm. of saline, it is evident that the venous pressure becomes approximately equal to the cuff pressure.

Fig. 7.—The relation between the increment in venous pressure produced by the compressing cuffs and the relative blood flow, as determined by the blood oxygen method in the experiments reported in Table II.

TABLE I. THE VENOUS OXYGEN CONTENTS IN THE EXPERIMENTS WITH 30 MM. HG PRESSURE (METHOD II)

SUBJECT	VENOUS OXYGEN CONTENT (VOLS. PER CENT)						ESTIMATED ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)
	EXPERIMENTAL ARM			CONTROL ARM			
	BEFORE PRESSURE 1	30 MM. PRESSURE 2	AFTER PRESSURE 3	1	2	3	
Gun.	12.87	10.51	12.30	13.30	13.05	12.48	18.5
Swe.	10.95	8.69	10.30	11.93	12.16	12.00	19.3
Ada.	9.52	7.87	9.66	9.14	8.50	9.25	16.8
Cro.	13.84	10.39	11.65	12.85	11.40	12.98	18.8
Atw.	10.93	8.96	10.45	10.62	12.45	12.51	18.7
Mean oxygen content	11.62	9.28	10.87	11.57	11.51	11.84	18.4
Standard deviation	1.72	1.14	1.03	1.70	1.78	1.49	1.0
Mean A-V differ- ence	6.8	9.1	7.5	6.8	6.9	6.6	
Mean hematocrit (per cent)	41.1	42.2	42.1	43.0	43.3	42.4	

Additional experiments with Method II were carried out on five subjects, from whom four successive pairs of blood samples were obtained at four- to five-minute intervals as follows: (1) before compression of the forearm; (2) during 20 mm. Hg pressure; (3) during 30 mm. Hg pressure; and (4) after release of the pressure. The hand circulation was occluded throughout the test. The individual results are presented in Table II, and the means in Fig. 5 (right). In every case there was a decrease in the oxygen content of the venous blood issuing from the forearm compressed at 20 mm. Hg, and a further decrease at 30 mm. Hg, resulting in an average decline in calculated blood flow of 25 and 34 per cent, respectively. Upon release of the pressure, the initial values were restored. All these changes had high statistical significance, with P values of less than 0.01. The changes in the control arm were small and not significant (P values were 0.66 to 0.79).

The average venous pressures under the compressing cuffs are shown in Fig. 6. These were determined, with the hand circulation occluded, before compression of the forearm, and at 10, 20, and 30 mm. Hg pressure on the forearm. The venous pressure under the cuffs during compression of the forearm promptly rose approximately to the cuff pressure. The indirect relationship between blood flow (estimated from the venous oxygen content) and the mean venous pressure is shown in Fig. 7.

Control Experiments: Ten control experiments were performed following the preceding procedure, with the exception that no pressure was applied to either forearm. Fig. 8 shows the average results, comparing the venous oxygen

TABLE II. THE VENOUS OXYGEN CONTENTS IN THE EXPERIMENTS WITH 20 AND 30 MM. HG PRESSURE APPLIED SUCCESSIVELY (METHOD II)

SUBJECT	VENOUS OXYGEN CONTENT (VOLS. PER CENT)								ESTIMATED ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)
	EXPERIMENTAL ARM				CONTROL ARM				
	BEFORE PRESSURE 1	20 MM. PRESSURE 2	30 MM. PRESSURE 3	AFTER PRESSURE 4	1	2	3	4	
Wai. McG. Kel. Tho. Gor.	9.13 13.89 13.41 13.07 7.22	7.08 13.04 11.30 11.75 4.87	5.90 11.86 10.35 10.83 4.16	9.70 14.67 12.79 13.55 6.58	10.56 13.10 15.30 12.25 6.22	10.56 13.24 14.87 12.94 5.48	9.86 12.72 14.25 12.78 6.65	9.66 13.03 14.70 12.90 6.19	16.0 19.0 16.8 19.3 12.1
Mean oxygen content	11.34	9.61	8.62	11.46	11.49	11.42	11.25	11.30	16.6
Standard deviation	2.98	3.47	3.38	3.29	3.40	3.66	3.02	3.39	2.9
Mean A-V difference	5.3	7.0	8.0	5.2	5.2	5.2	5.4	5.3	
Mean hematocrit (per cent)	41.2	41.3	41.3	41.1	41.1	41.2	41.1	41.1	

contents of three successive samples taken at 4 to 5 minute intervals from the right forearm with corresponding ones from the left forearm. Little change is evident in the mean data for either side. The individual data presented in Table III, however, show that fairly large spontaneous changes in venous oxygen content did occur in many control experiments. Since the direction of the change varied from test to test, the averages remained fairly constant. The mean changes were not statistically significant, as shown by the *P* values of 0.26 to 0.79.

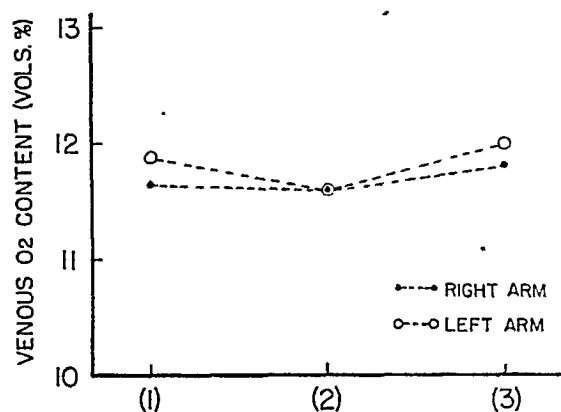


Fig. 8.—The mean results of the control experiments, showing the venous oxygen contents of three samples taken at four- to five-minute intervals from each arm. No pressure was applied to either forearm. The individual data for this group of ten subjects are shown in Table III.

TABLE III. THE VENOUS OXYGEN CONTENTS DURING THE CONTROL EXPERIMENTS—INDIVIDUAL DATA

SUBJECT	VENOUS OXYGEN CONTENT (VOLS. PER CENT)						ESTIMATED ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)
	RIGHT ARM			LEFT ARM			
	1	2	3	1	2	3	
Net.	11.02	9.92	12.20	11.74	10.22	12.47	20.2
Wac.	8.18	9.53	8.39	8.40	9.23	8.66	17.5
Ben.	13.34	13.32	13.33	14.24	13.38	13.83	20.7
Cra.	10.91	11.48	10.48	10.68	10.69	10.77	20.2
Wor.	10.94	11.31	12.51	12.63	14.47	14.57	20.2
Cri.	16.22	16.65	15.94	14.60	13.63	13.89	22.8
Hat.	10.10	9.78	11.42	10.97	11.56	13.09	20.0
Jon.	12.08	12.04	9.95	12.53	11.19	10.03	21.3
Lup.	13.96	12.65	13.83	12.29	10.99	12.42	17.3
McG.	9.94	9.36	10.27	10.56	10.59	10.23	17.0
Mean oxygen content	11.67	11.60	11.83	11.87	11.60	12.00	19.7
Standard deviation	2.31	2.24	2.20	1.84	1.68	1.97	1.9
Mean A-V difference	8.0	8.1	7.9	7.8	8.1	7.7	
Mean hematocrit (per cent)	43.7	43.8	43.5	43.9	43.6	43.8	

The spontaneous changes in venous oxygen content tended to be parallel in the two arms, supporting the validity of using one arm as a control against the other in the pressure experiments. Thus, the following correlation coefficients (r) between simultaneous changes in the two arms were computed by the product-moment method: for the change from the first to the second samples, $r = +0.57$; the second to the third, $r = +0.81$; the first to the third, $r = +0.93$. (A perfect positive correlation coefficient is 1.0.)

Plethysmographic Method.—In contrast with the preceding methods, the plethysmograph provides frequent *absolute* measurements of the blood flow. Repeated determinations may be made by intermittently obstructing the venous outflow from a limb, with a blood pressure cuff just proximal to the plethysmograph. During this time blood continues to flow into the part but cannot escape, thus causing the limb to swell. The displacement of the fluid surrounding the limb in the plethysmograph is recorded on a kymograph. The rate of increase of the limb volume is measured as the rate of blood flow.

Using a plethysmographic technique previously described,² measurements of the amount of blood flowing to the calf of the leg combined with that returning from the foot were made before, during, and after increasing the local pressure on the foot from 30 to 60 mm. of mercury. These pressures on the foot were produced by connecting the foot plethysmograph to a bottle inflated with air at the desired pressure. Measurements were made on six subjects. Almost uniformly, the combined blood flows decreased when pressure on the foot was increased and, conversely, increased when local pressure was decreased (Table IV). The occasional erratic results were attributed to large spontaneous vasomotor variations in blood flow that characteristically occur in the foot.

TABLE IV. THE EFFECT ON THE BLOOD FLOW OF VARYING THE LOCAL PRESSURE ON THE FOOT

	PER CENT OF DETERMINATIONS		
	BLOOD FLOW INCREASED	NO CHANGE	BLOOD FLOW DECREASED
Pressure increased from 30 to 60 mm. Hg (26 determinations)	7.7	7.7	84.6
Pressure decreased from 60 to 30 mm. Hg (24 determinations)	87.5	12.5	0.0

This method has the disadvantage that it is not possible to measure directly the blood flow in the compressed area, the foot. The measured values include the blood flow to the calf, which was not exposed to the pressure. A technique was therefore developed to measure the blood flow in the forearm while pressure was applied to this segment.

The technique employed in the experiments which will be described was as follows (see Fig. 9). A standard venous occlusion plethysmograph (*A*) was fitted on each forearm in the usual way.³ The one on the control arm was filled with water, leaving an air space of 150 c.c. which was connected directly with a recording bellows. The apparatus on the experimental arm was filled completely with water which was maintained at a temperature of 32° centigrade. To one of the lead-off holes was attached a large rubber tube (*C*), 1.5 cm. in diameter, connected at its other end with a two-liter aspirator bottle (*D*). The tube and bottle were filled with water, also leaving an air space of 150 c.c. which was connected through a rubber tube (*E*) with a second recording bellows (*F*).

Initially, the aspirator bottle was so placed that the water surface in the bottle was at the same level as that in the plethysmograph during direct recording, namely, 8.5 cm. above the center of the forearm. By raising the bottle, the hydrostatic pressure on the portion of the forearm in the plethysmograph could instantly be increased by any desired amount. Cuffs applied around the wrists just distal to the plethysmographs were inflated to a pressure greater than systolic during the determinations. Blood flow measurements were obtained by recording in the usual way the change in arm volume during inflation of the collecting cuff on the arm, just proximal to the plethysmograph. The collecting pressure was greater than that within the plethysmograph and below diastolic pressure, usually between 60 and 80 mm. of mercury. Repeated control measurements of the blood flow, as recorded through the aspirator bottle, were similar to the plethysmographic tracings obtained by the usual method from the same and the opposite arm, except for a decreased amplitude of the recorded pulse waves. The apparatus was calibrated by introducing water in 5 c.c. increments through the thermometer opening (*B*), and recording the rise of the tracing on the kymograph. The calibration was essentially the same when the aspirator bottle was elevated as when it was at the initial level, or when the plethysmograph was connected directly with the bellows.

Whenever the local pressure on the forearm was increased, the plethysmographic blood flows decreased, and, conversely, when the pressure was decreased the flows increased. A representative recording demonstrating the effect of a pressure increment of 20 mm. Hg is shown in Fig. 10.

A summary of the results and their statistical significance is presented in Table V. Immediately after a change in pressure on the forearm there was often a shift in the base line of the plethysmographic tracing, attributable to readjustment of the sealing cuffs and of the plethysmograph itself to the altered pressure. All calculations of blood flow were made on tracings taken after this effect had ceased. The table shows that even with a 10 mm. Hg increment in pressure the ensuing decrease in blood flow was statistically significant (*P* value, 0.03). With 20 and 30 mm. Hg, the statistical significance of the decrease in flow was very high (*P* values less than 0.01). The average changes in blood flow in the control arm were small, tending to be opposite in direction to those in the experimental arm, and lacking statistical significance.

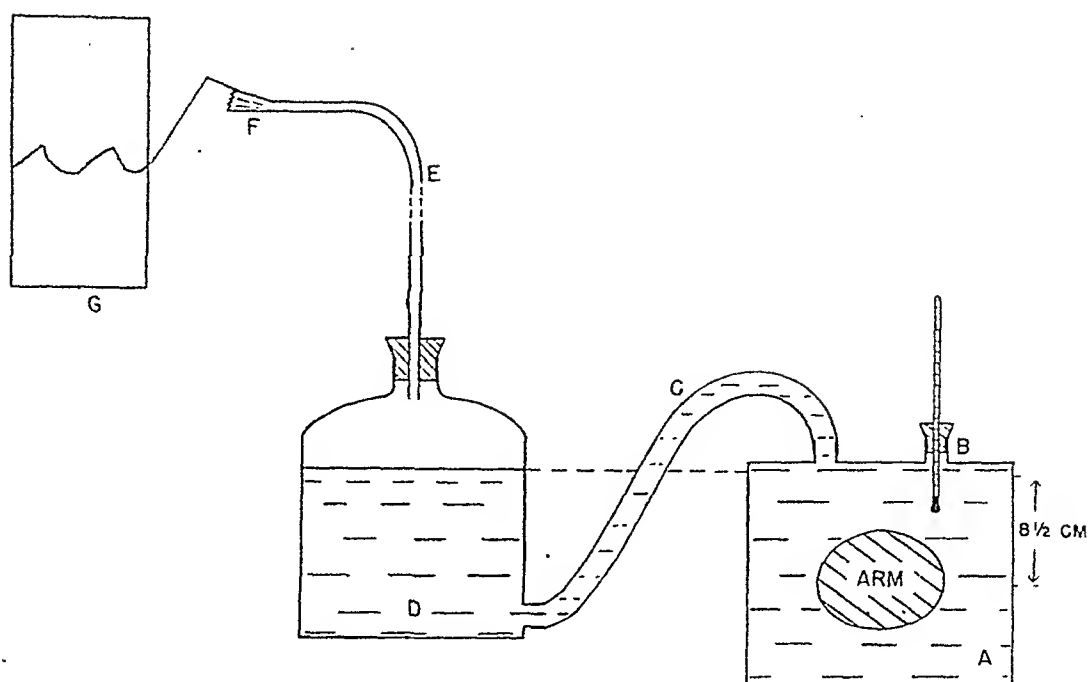


Fig. 9.—Diagrammatic representation of the apparatus used for the plethysmographic measurement of blood flow in the forearm during the application of local pressure. Symbols: A, plethysmograph; B, thermometer opening, also used for calibrating the system; C, 1.5 cm. bore rubber tubing; D, aspirator bottle; E, rubber tubing; F, recording bellows; and G, kymograph. By varying the height of the aspirator bottle, the desired hydrostatic pressure was applied to the segment of forearm in the plethysmograph.

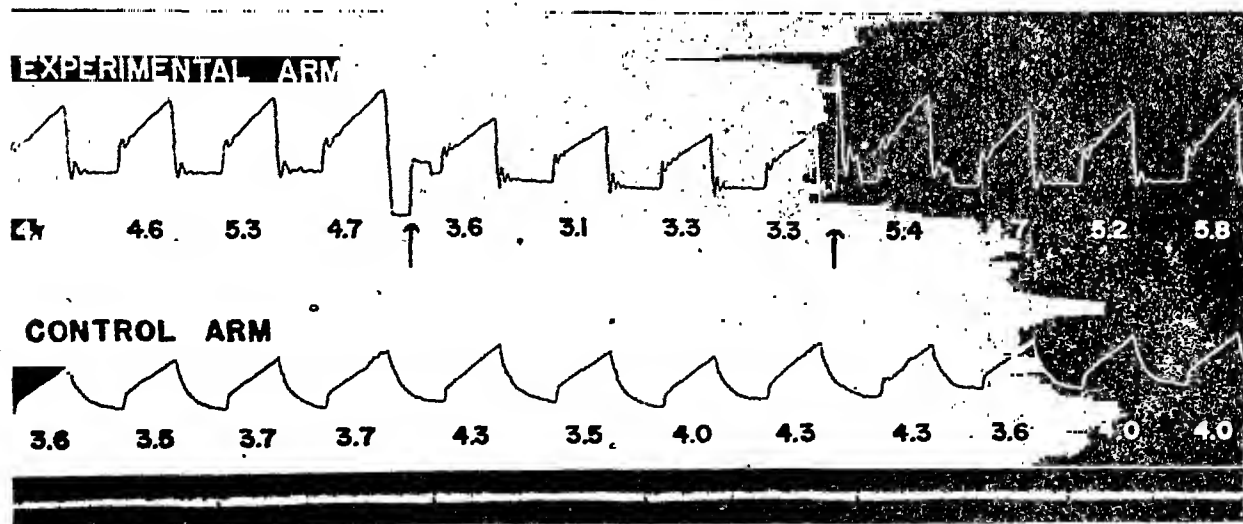


Fig. 10.—A typical plethysmographic recording of blood flow before, during, and after the application of 20 mm. Hg pressure on one forearm (upper tracing). The blood flow in the opposite (control) forearm, recorded simultaneously, is shown in the lower plethysmographic tracing. The time scale at the bottom indicates seconds.

TABLE V. THE EFFECT OF LOCAL PRESSURE ON BLOOD FLOW IN THE FOREARM—PLETHYSMOGRAPHIC DATA

ITEM	10 MM. HG INCREMENT IN PRESSURE (7 EXPERIMENTS)		20 MM. HG INCREMENT IN PRESSURE (11 EXPERIMENTS)		30 MM. HG INCREMENT IN PRESSURE (7 EXPERIMENTS)	
	EXPERI- MENTAL ARM	CONTROL ARM	EXPERI- MENTAL ARM	CONTROL ARM	EXPERI- MENTAL ARM	CONTROL ARM
Blood flow in c.c. per minute per 100 c.c. of forearm	Before pressure { Mean { S.D.	2.96 0.77	2.83 0.76	2.97 0.92	3.10 1.08	2.69 0.85
	During pressure { Mean { S.D.	2.69 0.83	3.07 1.01	2.16 0.70	1.53 0.56	2.89 0.81
	After pressure { Mean { S.D.	3.25 0.73	2.90 0.96	3.10 1.11	3.01 1.12	2.89 0.74
Statistical significance of changes in blood flow	On applying pressure { Mean change P*	-0.28 0.03	+0.24 0.13	-0.81 <0.01	-1.57 <0.01	+0.20 0.09
	On removing pressure { Mean change P*	+0.56 <0.01	-0.17 0.27	+0.94 <0.01	+1.49 <0.01	0.00 0.91

*P is the probability that the change is due to chance. Values of 0.05 or less indicate statistically significant changes.

These results could not be compared directly with those of the blood gasometric method for the following reasons. In the latter method the initial pressure on the arm was zero (atmospheric). This was not true in the plethysmographic method, where the initial pressure was 8.5 cm. H₂O (or 6 mm. Hg), to which the various increments in pressure were added. It was necessary, therefore, to estimate by graphic extrapolation the blood flow at zero pressure, and by interpolation the flows at 10, 20, and 30 mm. Hg above atmospheric. The way in which this was done is shown in Fig. 11, where the blood flows, in terms of the initially measured rate (which was given an index value of 100), are plotted against pressure *above atmospheric*. The extrapolated blood flow at zero pressure was thus 106, and the interpolated flows at 10, 20, and 30 mm. Hg pressure above

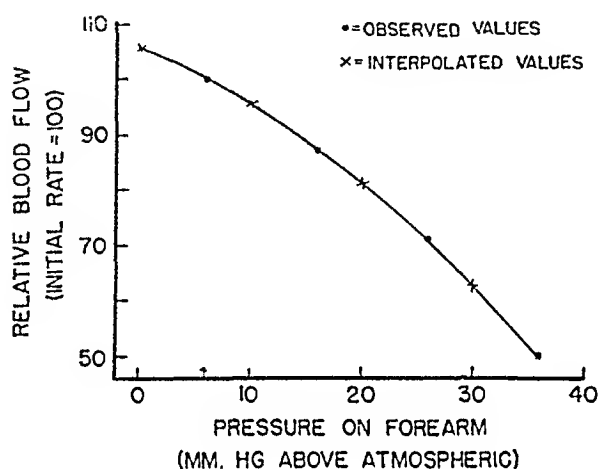


Fig. 11.

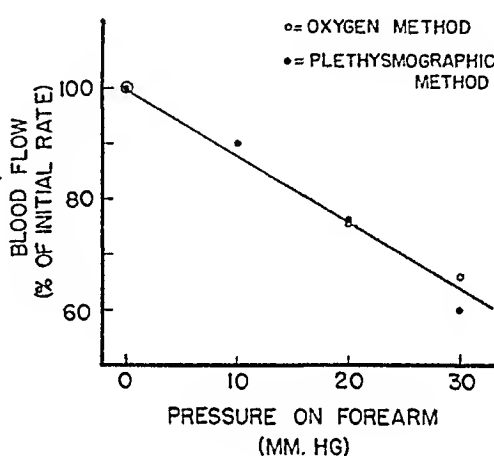


Fig. 12.

Fig. 11.—Graphic interpolation of plethysmographic blood flows at true pressures (related to atmospheric pressure) of 0, 10, 20, and 30 mm. of mercury. The arrow on the horizontal scale, at 6 mm. Hg, denotes the mean hydrostatic pressure at which the initial blood flow measurements (given an index value of 100) were made, and to which the various pressure increments were added. The observed values were calculated from the data in Table V.

Fig. 12.—A comparison of the effect of local pressure on the blood flow in the forearm by the blood gasometric (Table II) and plethysmographic methods. The blood flow at zero (atmospheric) pressure is given an index value of 100 in each case.

atmospheric were 95, 81, and 63, respectively. Therefore, at 10 mm. Hg above atmospheric the blood flow was reduced to $95/106 = 90$ per cent of that at zero pressure; at 20 mm. Hg, to $81/106 = 76$ per cent; and at 30 mm. Hg, to $63/106 = 60$ per cent. As shown in Fig. 12, these values were approximately equal to those calculated from the venous oxygen method on the assumption that the rate of oxygen utilization remained constant. This finding confirms that assumption.

DISCUSSION

While it was obvious that a reduction in blood flow would occur in an extremity during local compression of considerable degree, it was not known how little compression is necessary to produce this effect. The problem had already

been partly investigated by Darling and Belding,¹ whose purpose was to evaluate the role of pressure by foot gear in the development of trench foot. Their method consisted of measuring the skin temperature of various parts of the foot while the subject was in a cold room (6°F. or 4° F.). They found that when a pressure of 50 mm. Hg or more was applied to one foot by means of a pneumatic stocking, it cooled more rapidly than did the opposite foot, which was not compressed. No consistent differences were obtained with pressures lower than 50 mm. of mercury. The authors indicated, however, that their method may not have been sufficiently delicate to detect small changes in blood flow, and also that the intense vasoconstriction in the cold environment may have masked the effects of lower pressures.

In the present study it was shown that increments in local pressure as small as 10 mm. Hg were sufficient to reduce definitely the circulation in normal limbs. These results, obtained by three different methods, demonstrate the importance of small degrees of local compression. Thus, pressure on the extremities, such as those ordinarily produced by snug clothing, gloves, shoes, bandages or splints, or by the weight of the limbs themselves, or even of the bed clothes upon the bony prominences may be sufficient to reduce significantly the circulation in the compressed parts of normal limbs. In patients with peripheral vascular disease, such reduction of blood flow may produce serious results. The importance of these findings both in medical and surgical cases seems obvious.

The mechanisms by which blood flow is reduced during local compression are interesting to speculate upon. Certainly, one factor is the reduction of the pressure gradient between the arteries and veins as demonstrated by the prompt rise in venous pressure approximately to that in the compressing cuffs. Another possible mechanical factor involved in the reduction of blood flow is the decrease in the caliber of the small vessels in the compressed area causing an increase in resistance to flow.

SUMMARY

The effect of locally applied pressures of 10 to 50 mm. Hg on the extremities was investigated by three methods: (a) thermometric; (b) blood gasometric; and (c) plethysmographic. The results indicated that local pressures of remarkably low amounts may impair the circulation. Skin temperature measurements showed a definite effect with pressures as low as 20 mm. of mercury. At this pressure, the arteriovenous oxygen difference rose about 25 per cent, and plethysmographic tracings showed an equal decline in blood flow. With a local pressure of 30 mm. Hg, the blood flow decreased about 25 per cent as measured both by the blood gasometric and the plethysmographic methods. Even at 10 mm. Hg the plethysmograph revealed a 10 per cent decline in blood flow.

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THE FUNCTIONAL PATHOLOGY OF EXPERIMENTAL IMMERSION FOOT

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THE abundant literature on trenchfoot and frostbite which appeared after the first World War, and especially after the second World War, is full of contradictory statements. Those students of the subject who go somewhat deeper into the question of the functional pathology of the two lesions, or as many authors like to state, one lesion, can be divided into two opposing groups. One group, under the leadership of Ungley and Blackwood,¹ feels that in the immersion foot syndrome all lesions due to cold, including frostbite, are due mainly to a peripheral vasoneuropathy, almost all of the pathology being located in the muscle and nerve tissue. The other group, under the leadership of Greene,² Friedman,³ and Siegmund,⁴ believes that the lesions of frostbite, as well as of immersion foot syndrome, are caused by intravascular agglutinative thrombi as we^{5,6} and others have demonstrated in actual cases of frostbite and in experimental frostbite.

Kreyberg,⁷ with his deep understanding of the functional pathology of the lesions due to cold, tries to differentiate clearly between the lesions due to moderate but protracted cold in a wet surrounding (immersion foot) and the lesions due to intense but short-lived exposure in a surrounding of air (frostbite). All conclusions concerning immersion foot are drawn from analgy, as Kreyberg⁷ states, since actual observations during the exposure and immediately thereafter are almost completely missing and since the biopsy material is confined almost exclusively to gangrenous areas.

We felt, therefore, that it is essential to produce trenchfoot in experimental animals to permit the study of the functional pathology and to determine whether therapeutic measures such as heparinization, which we found successful in frostbite, are applicable to trenchfoot lesions. There is only one report in the literature, by Smith and associates,⁸ in which an attempt was made to produce trenchfoot experimentally and their results were rather doubtful.

After numerous difficulties, we were able to produce in rabbits a constant lesion comparable to immersion foot (Fig. 1).

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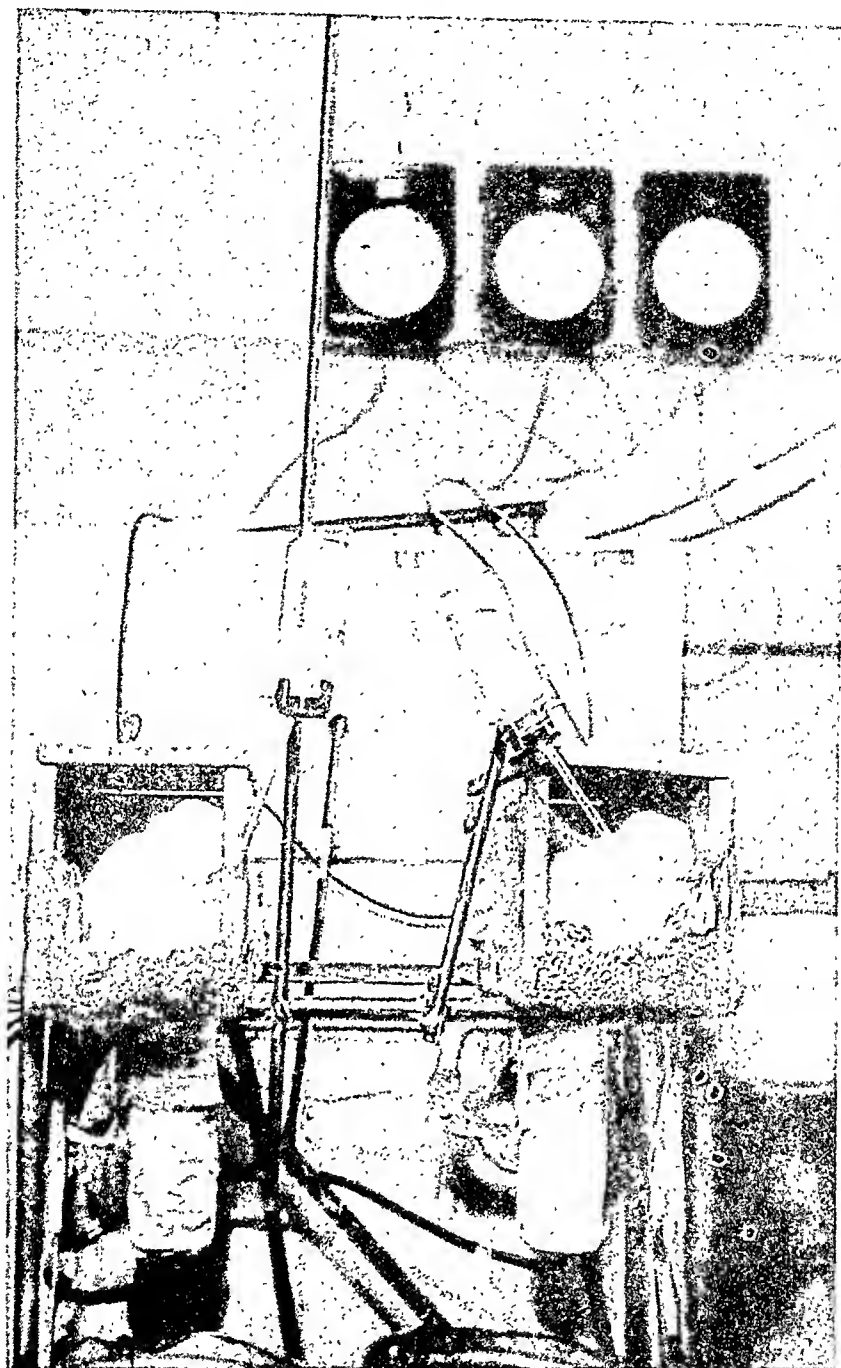


Fig. 1.—Two rabbits in experimental setup for the production of trenchfoot. The cylinder from the right foot is removed to make the position of the animal visible.

EXPERIMENTAL METHOD AND OBSERVATIONS

A female adult rabbit is placed in a rabbit box with both hind legs projecting through holes in the floor and into two aluminum cylinders fastened to the bottom of the box. The left cylinder is closed at the bottom except for an inlet for water, and has an outlet near the top. Water constantly enters this cylinder containing the left hindleg of the rabbit from a tube, which siphons it from a reservoir through coils into the cylinder and is removed through the outlet by a pump which returns it to the reservoir. The coils are placed in the tank of a cooling unit which per-

mits an exact control of the temperature of the water entering the cylinder. A recording thermometer in the cylinder records the temperature of the water throughout the experiment. The temperature does not vary more than 2°F. during the entire exposure. The animals are prevented from escaping by two straps holding them down in the box.

All experiments last for three to four days, during which time the animals are fed and watered unless starvation is part of the experiment. The rectal temperature, respiratory rate, and electrocardiogram are taken at regular intervals. The opposite leg is not cooled but held in a similar cylinder without water to see the effect of immobility and dependency. Thermocouples are inserted into the exposed leg during the exposure in certain experiments.

At temperatures between 3 and 5° C., one is able to make the following observations: After immersion, the temperature of the exposed limb goes down rapidly but does not reach the temperature of the surrounding water even after several days, indicating the persistence of some circulation in the limb (Fig. 2). If fluor-

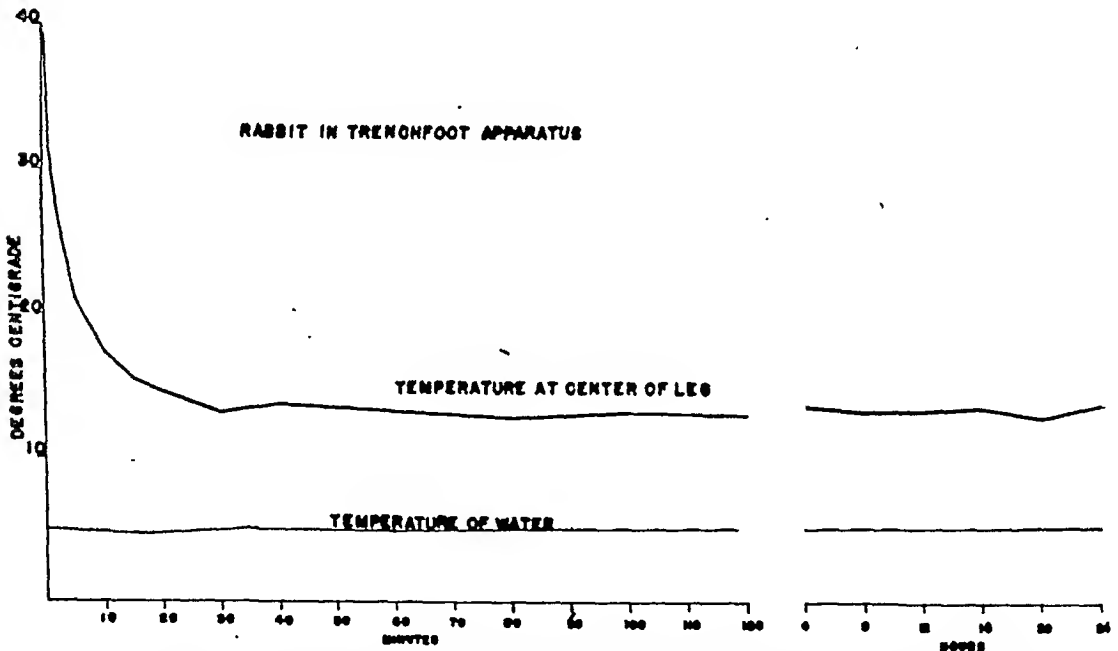


Fig. 2.—Temperature near the tibia of the left calf in a rabbit in the trenchfoot apparatus and the temperatures in the water surrounding this leg.

escein is given into the ear vein one will notice that, in contrast to exposures to subzero temperatures, as in frostbite, the dye always appears in the exposed limb, although markedly delayed and in lower concentration compared with the nonexposed limb. Severe swelling occurs *during* the exposures; it is quite noticeable after twenty-four hours, and is severe after forty-eight hours of exposure. It extends all through the exposed part of the limb. The appearance of swelling *during* the exposure is in direct contrast to frostbite, where the swelling occurs *after the end* of the exposure. This, again, indicates that during the immersion the circulation is not completely interrupted, for only in the presence of a positive filtration pressure in the vascular system can edema occur. The nonexposed leg



Fig. 3.—Severe swelling of left calf and toes of a rabbit exposed for ninety-six hours to water at a temperature of 3° centigrade. One day after exposure.

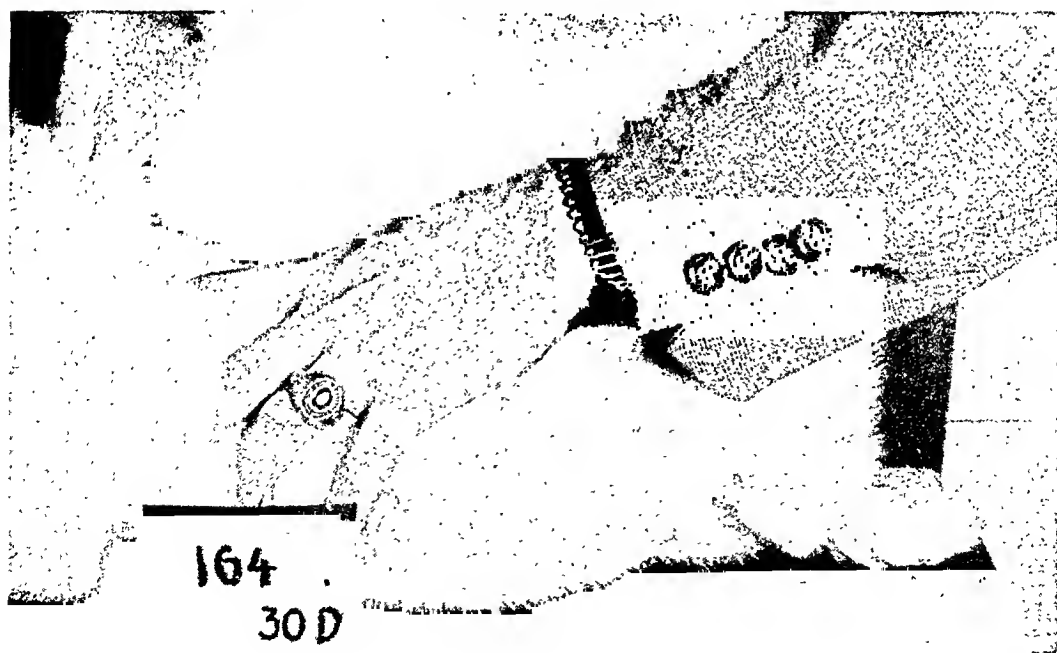


Fig. 4.—Rabbit thirty days after exposure of the left leg for ninety-six hours to a temperature of 3° centigrade. Note dragging of the left leg.

also shows some swelling due to the dependency, but this is present only over the toes and is not of the same order of magnitude as the swelling in the exposed leg. When removed from the device after three days of exposure, the temperature in the depth of the exposed leg rises immediately and rapidly, reaching body temperature within thirty minutes. The leg is severely swollen and the animal is unable to use the leg due to a flaccid paralysis. Muscular tone has disappeared; passive movement is possible without resistance, pinprick produces no reaction and the leg is dragged (Figs. 3 and 4). A fluorescein test performed at this time shows maintenance of a slow but positive circulation. After three to six hours, the leg becomes markedly hyperemic and hot. A fluorescein test⁹ performed at this time shows a marked hyperfluorescence due to the increased capillary permeability.

After forty-eight hours the swelling of the leg has disappeared, the hyperemia has become moderate, and the hyperfluorescence has decreased. The swelling over the toes in the nonexposed leg disappears within four hours after the end of the exposure. The exposed foot is dropped when the animal is lifted up and the animal is apparently unable to spread its toes, leading to a characteristic appearance of the foot (Fig. 5). There is no reaction to pinprick or tapping of the Achilles tendon. The animal cannot use this leg and drags it when walking. All of these signs persist for from four to ten weeks in most animals. They are usually combined with a marked atrophy of the muscles of the foot and the calf. The characteristic foot drop and the inability to spread the toes are the most persistent signs. This inability to spread the toes is also a very characteristic and persistent sign of human trenchfoot lesions. The animals favor the opposite leg for many weeks although the skin has returned completely to normal. The regrowth of the clipped hair is not slower on the exposed side than on the nonexposed side (Fig. 6). The circulation time and capillary permeability return to normal in four to five days and the reaction to pinprick usually returns after four to five weeks.

It was most astonishing that of the seventy-five animals subjected to the exposure, of which twenty-eight survived the seventh day after exposure, none showed any gangrene except in areas of superimposed trauma or infection.

In order to exclude the water without the lowered temperature as the cause of the swelling and the muscular and neurological phenomena, the legs of five animals were exposed in the cylinder to water at body temperature. They showed a fleeting swelling similar to that found in the legs with dependency only, but after twenty-four hours, there is complete restitution of normal function and shape of the leg.

Morphologic studies of the limbs of animals sacrificed at varying intervals are being carried out* and will be reported in the near future. One thing is outstanding, however: in none of the specimens of trenchfoot animals of any stage can one discover the agglutinative thrombi of red cells which are so characteristic of true frostbite. The histologic lesions seem to be confined to the muscles and predominantly to the nerve tissue, in which severe degenerative changes can be

*In collaboration with Dr. N. B. Friedman of the Army Institute of Pathology.

found for weeks following the exposure. There is an excellent correlation between the nerve lesions and the functional disturbances. They are completely different from the lesions seen in frostbite.

It is, therefore, obvious that the treatment by heparinization for six to ten days which we described to prevent gangrene subsequent to frostbite is not applicable in trenchfoot. It should be mentioned here that in frostbite the heparinization has to be continuous and persistent. The failure to obtain results recently reported by Quintanilla and associates¹⁰ was due to heparinization for only thirty-six hours.



Fig. 5.—Foot drop and inability to spread the toes in the left leg of a rabbit. The leg was exposed for ninety-six hours to a temperature of 3° centigrade. Three days after exposure.

It is interesting to speculate as to the actual cause of the lesions in trenchfoot. By introducing a thermoneedle into the vein carrying the blood from the exposed leg, one notices that the temperature of this blood is almost identical with the internal temperature of the exposed leg. At a temperature of 6° to 8° C., however, the oxygen dissociation of the blood is extremely low.¹⁴ Although

one can assume that the tissue metabolism is also at a very low level, the fact remains that there exists almost complete tissue anoxia for as long as several days. The slow speed of the blood stream in such a limb contributes further to the anoxia. The blood returning from such a limb is bright red and shows no apparent oxygen depletion. The skin of the leg itself appears bright pink due to the lowered dissociation. In order to see whether these factors lead to a local histamine production which, in turn, produces the increased capillary permea-



Fig. 6.—Same animal as in Fig. 5 three weeks after exposure. Note the same neurological lesions but the extensive regrowth of hair.

bility, we kept two animals on high doses of pyribenzamine during the entire length of the experiment. They did not show any diminution of swelling as compared to the other animals. The fluoroscein tests done during the first twenty-four hours after exposure indicate an increase in permeability in the exposed as compared with the nonexposed side. This increase is, however, much less intense than that seen after exposure to frostbite; it is less intense as well as less

persistent. It is, therefore, understandable that the loss of plasma which leads to the typical stranding of red cells and the silting up of the capillaries with subsequent agglutinative thrombi in frostbite cannot be found in trenchfoot and that, therefore, the subsequent intravascular phenomena are missing.

Of our group of seventy-three animals thus exposed, eight showed a marked lowering of body temperature twenty-four to seventy-two hours after the onset of exposure. It appeared that in the face of the continuous heat withdrawal from the one leg, they were not able to maintain their body temperature. In these animals a typical sequence of events occurred.

At first, when the body temperature has dropped to 32° to 33° C. the pulse rate rises, the animals become very irritable, and seem to have an unstable gait when taken out of the box. Further slow lowering of the body temperature to approximately 28° C. produces considerable drowsiness. The respiration and the pulse rate become progressively slower until death occurs at a body temperature of approximately 24° centigrade.

During the last phase of lowered temperature, between 24° and 28° C., marked electrocardiographic changes may be found. Deep depressions of the S-T segments in all leads are followed by an elevation of the S-T segments with inverted T waves as seen in myocardial infarctions (Fig. 7). Morphologic ex-

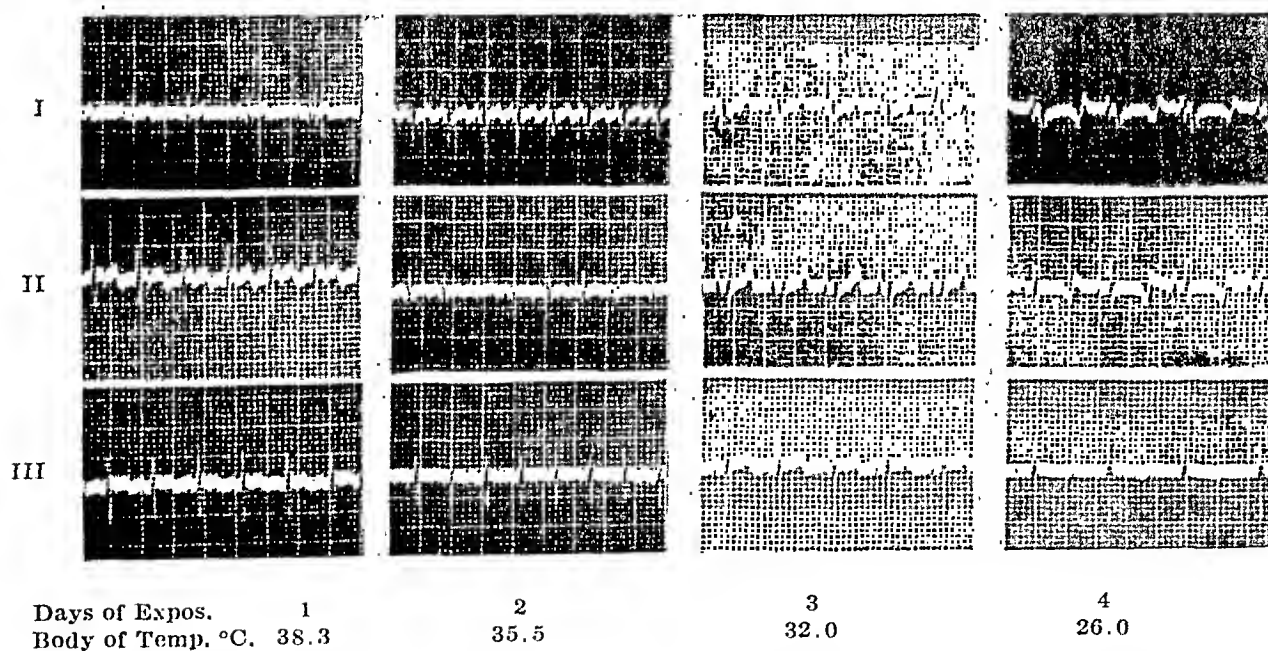


Fig. 7.—Electrocardiograms of a rabbit during trenchfoot exposure with general loss of body temperature.

aminations of such hearts, however, have thus far failed to reveal any specific lesion. In two animals we succeeded in promptly reversing these electrocardiographic changes by rapidly raising the body temperature by means of hot baths and warm saline enemas. Nevertheless, these animals died.

These findings, which require further study, may explain certain cases described in the German,¹¹ British,¹² and recently, in American literature,¹³ in which survivors of shipwreck showed marked disturbances in cardiac rhythm,

and sometimes sudden death during an apparently uneventful recovery. The mechanism may possibly be explained by the prolonged myocardial anoxia produced by the diminished oxygen dissociation. It is possible that we have seen more of such disturbances than other observers, since our experiments lead to a slow and gradual lowering of body temperature whereas other observers were using experiments directed toward an acute, rapid lowering of body temperature.

SUMMARY AND CONCLUSIONS

In conclusion, we wish to state that the lesions in experimentally produced trenchfoot are basically different from those in frostbite. They consist mainly in disturbances of muscular and nervous function. Intravascular agglutinative phenomena characteristic of frostbite are missing.

In contrast to frostbite, the circulation in the exposed limb continues during the immersion, although it is slower and diminished in amount. Edema in trenchfoot occurs, therefore, *during* the exposure whereas in frostbite it occurs some time *after* the exposure.

The increase in capillary permeability is much milder in trenchfoot than it is in frostbite.

Gangrene subsequent to experimental trenchfoot lesions is extremely rare and occurs only when pressure or local infection are superimposed.

The lesions in trenchfoot seem to be a consequence of the protracted tissue and especially nerve anoxia, while in frostbite the main part of the damage is due to intravascular agglutinative thrombi.

The tissue anoxia due to lowered oxygen dissociation seems also to be the cause of severe electrocardiographic changes in animals in which the body temperature is lowered due to the trenchfoot exposure.

It is possible and even probable that the two lesions may overlap or coexist in individuals exposed to sudden extreme cold during a long exposure to immersion foot conditions, or in individuals who have a great tendency to vascular spasm. Such individuals may react with a complete vascular shutdown, as seen in frostbite, when normal individuals still maintain a certain amount of circulation. Usually it is the extreme cold, with complete circulatory standstill in the exposed part, which causes the severely increased capillary permeability leading to stranding of the red cells in the capillaries.

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THERAPY DIRECTED AT THE SOMATIC COMPONENT OF CARDIAC PAIN

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THE idea that visceral pain may be relieved by local anesthesia of the somatic tissues concerned in the reference of pain is not new. Nearly twenty years ago this fact was demonstrated by Weiss and Davis¹ in twenty-five cases of visceral disease, which included two of heart disease. However, the therapeutic import of their observations became lost in the issues which developed as to the theoretical role of the so-called "somatic reference zone" in the mechanism of visceral pain reference.

We likewise have found that local block of afferent neural impulses from the somatic structures which mediate referred visceral pain may relieve pain due to heart disease under suitable conditions.² This report deals with the demonstration of this fact, and with practical aspects of local block therapy directed at the somatic component of cardiac pain.

CLINICAL DATA

We have studied thirty-one patients with chest pain due to coronary artery disease, who presented trigger areas in the voluntary muscles, and in whom an attempt was made to block the noxious impulses from these abnormal foci either by local procaine infiltration or by ethyl chloride spray. These observations on pain of cardiac origin have been oriented against a background of experience in a larger number of patients with chest pain and somatic trigger areas activated by disorders of the skeletal muscles rather than by heart disease.

The common denominator of cardiac and somatic chest pain in these subjects is the presence of a trigger mechanism in the somatic structures. It is, therefore, necessary first to define the abnormal zone of hypersensitivity known as a trigger area. Its essential characteristic is that when it is stimulated by pressure or needling, it gives rise to a brief reference of pain. The referred pain is usually perceived at a distance from the trigger area, but as in the case of the precordial muscles, it may circumscribe the trigger area itself.^{3,4} In either case, the spread of pain represents a true reference phenomenon, since it does not conform to an area supplied by a peripheral nerve.

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The distribution of pain referred from trigger areas is relatively constant for the site of origin; thus, similarly located trigger areas in different individuals produce similar, and therefore, predictable pain reference patterns.^{5,6} As a consequence, in skeletal muscle disorders without organic heart disease, the appropriate trigger areas give rise to referred pain which is indistinguishable in distribution and quality from the substernal and radiating pain of coronary insufficiency.

Although trigger areas reside occasionally in the skin, we have found them to be located in most instances within the myofascial structures. It is not known what tissue within the muscle mass becomes physiologically altered so as to constitute the trigger area, but we have observed that in the process of biopsy of a trigger area without anesthesia (except morphine), lightly touching, lifting, or pinching the outer fibrous sheath of the muscle at this spot momentarily reproduced the specific pattern of pain reference which characterized this trigger area and which had been previously elicited by pressure.

LOCATION OF TRIGGER AREAS

Muscles which frequently develop trigger areas in association with coronary artery pain are the pectoralis major and minor and the serratus anterior. The patterns of referred pain induced by mechanical stimulation (needling) of trigger areas in these and other muscles of the chest and shoulder girdle have been mapped both in the presence and absence of heart disease. As has been implied, the patterns are similar whether the trigger mechanism is activated by cardiac or somatic factors.

It has been found that trigger areas in the myofascial structures of the parasternal region give rise to pain perceived chiefly beneath the sternum. Trigger areas in the lateral part of the precordium, where the pectoralis major and minor muscles overlap, give rise to pain widely distributed over the precordium, occasionally referred to the scapula and frequently to the medial epicondyle of the elbow and ulnar distribution in the forearm and hand. Trigger areas in the inferior margin of the pectoralis major muscle at its mid-point include the nipple and breast in their reference pattern. Trigger areas close to the ribs in the lowest slips of the pectoralis minor muscle at their origin often produce pain located deep within the chest and described as "inside the heart." Trigger areas anterior to the sternum in the rudimentary sternalis muscle give rise to a reference of pain which may extend up and down from the base of the neck to the epigastrium. Trigger areas in the axillary region in the serratus anterior muscle induce a spread of pain at the corresponding level which travels anteriorly almost to the sternal border and posteriorly as far as the interscapular line, and occasionally to the volar aspect of the arm as far as the palm. Trigger areas in the serratus muscles are apt to cause pain on deep inspiration, or a sense of constriction of the chest.

With a precise knowledge of these reference patterns, the search for trigger areas is facilitated if the patient gives a clear description of the location of spontaneous pain. However, the essential part of the examination is the discovery by careful palpation of discrete areas of exquisite tenderness. Thus, the examiner

may suddenly locate a small spot of hyperalgesia so acute that the patient winces when it is palpated. The hyperalgesia may be cutaneous, but usually it represents a hypersensitivity of the deeper structures. This is shown by the fact that the skin may be lifted off the deeper structures and compressed without inducing pain, whereas even light pressure against the skin when it is in contact with the underlying structures elicits a painful response.

When an extremely sensitive trigger area is stimulated by pressure, the patient usually describes a reference of pain clearly perceived at a distance. On the other hand, if the spread of pain induced by pressure circumscribes the trigger area, the subject may fail to distinguish the reference of pain from the local hyperalgesia at the trigger area itself. With the stronger stimulus of needling the trigger area, however, the reference pattern is usually sharply delineated.

LOCAL BLOCK TECHNIQUES

Local Infiltration.—Since the relief of pain by so-called "analgesic" injection is not dependent on the local anesthetic action of a drug,⁷ the concentration of procaine hydrochloride in physiologic saline has been reduced for infiltration to 0.25 to 0.5 per cent. One reason for using any procaine at all is that even such low concentrations appreciably reduce the immediate pain induced by the infiltration.

The patient is questioned regarding sensitivity to procaine, and if a history of allergy is obtained or if the patient has never before received procaine, either physiologic salt solution is used for injection, or an initial test dose of 5 to 10 mg. of procaine hydrochloride is given by muscle and the patient observed for ten minutes for a general reaction. The total dose of procaine hydrochloride at the first treatment is limited to 100 mg. and is stepped up gradually at subsequent treatments if necessary. If the patient is unduly apprehensive and has not received previous sedation, a preliminary dose of a rapidly acting barbiturate is given by mouth.

In infiltrating trigger areas in the muscles, it is not necessary to infiltrate the skin. There is also no need to withdraw on the plunger of the syringe to determine whether the point of the needle lies within a blood vessel if dilute solutions of procaine are used and if infiltration is performed with the needle constantly moving in or out. The needle is kept in motion in order to reach as many muscle layers as possible, and also to avoid introducing more than a drop or two of the procaine solution into a blood vessel, if one were entered. Furthermore, the intravenous injection of procaine in the nonallergic individual no longer connotes the same hazards as formerly, and is being widely used by this route in a variety of clinical conditions.^{8,9}

The depth of injection depends on the site of the trigger area. At the sternal borders, the musculature is thin and the trigger areas therefore superficial. Laterally, the pectoral muscles are thicker and the trigger areas may be fairly deep, especially where the thoracic cage falls away from the skin surface. Therefore, in a muscular person it may require a two inch needle (23 gauge) to infiltrate a trigger area in the pectoralis minor muscle. For more superficially located

trigger areas in the pectoralis major and serratus muscles, a one to one and one-fourth inch needle (24 gauge) is used. The needle should not be inserted up to the hilt because of the difficulty of extraction in case of breakage. It should be inserted at a tangent to the ribs to assure that the pleural cavity is not penetrated.

For a given trigger area the amount of solution injected is usually about one to four cubic centimeters, but less may suffice. If local tenderness at the trigger area is not abolished, reinjection of the same area at a different depth or angle is employed.

Pyrogen-free solutions are used. When pyrogenic materials are injected into trigger areas, intense afterpain may result.

Ethyl Chloride Spray.—A technique somewhat modified from that recommended for sprains¹⁰ is employed. A standard glass container, preferably with a nozzle which delivers a fine spray, is used. The tube is held about two feet from the patient. The spray is applied not perpendicularly, but at an acute angle or even at a tangent to the surface of the skin. It is applied with a constant rotary motion of the wrist so as not to concentrate it in a small area. The spray is usually applied for about five to fifteen seconds at a time; it is discontinued if the skin becomes blanched. Frosting is to be avoided; if frost appears, it is promptly wiped off.

To avoid inhalation of ethyl chloride vapor, an adequate circulation of air is desirable. Since the vapor is heavy and travels downward, it is preferable that the spray should be applied with the patient sitting up, or at least propped up with pillows. The usual precautions for the handling of a volatile inflammable substance should be observed.

Spraying is continued at brief intervals until the spontaneous pain has disappeared. If pain persists, this procedure is stopped after about ten to fifteen minutes.

If ethyl chloride spray fails to relieve pain, local infiltration of the trigger areas may be tried. One should, however, await the return of the skin to room temperature because ecchymosis has followed immediate needling of a heavily sprayed area.

RESULTS

The thirty-one subjects with pain due to inadequacy of the coronary circulation were classified into three groups: Group 1, subjects with constant chest pain initiated by an acute myocardial infarct and no pain prior to this event (four patients); Group 2, subjects with effort angina associated with antecedent or intercurrent myocardial infarction (eighteen patients); and Group 3, subjects with effort angina uncomplicated by a known myocardial infarct (nine patients). We shall omit from consideration the results of local block therapy in those other patients with chest pain who had equivocal or no evidence of coronary artery disease.

Patients With Constant Chest Pain.—The patients in Group 1 provided the most convincing demonstration that cardiac pain may be blocked at the somatic

component. Table I shows the results obtained in four subjects who had five myocardial infarcts and prolonged substernal or precordial pain following each of these events, but no anginal pain previously. The duration of pain prior to treatment ranged from four hours to twenty-one days. One of these patients (I. C.) had marked hypertension (200/110).

Complete relief of the protracted pain was secured in all instances, either by local procaine infiltration of the trigger areas in the precordial muscles, or by ethyl chloride spray of the discrete tender areas in the precordium, or by a combination of both procedures. In four infarctions, complete relief was immediate, and one treatment sufficed to secure a permanent result. In one infarction, temporary amelioration of pain occurred after the first local block, but four such treatments were necessary to obtain lasting complete relief.

Two of these cases with persistent chest pain following acute myocardial infarction are presented in detail. (Cases 1 and 2.)

TABLE I. RESULTS OF LOCAL BLOCK THERAPY IN CONTINUOUS CHEST PAIN INITIATED BY A MYOCARDIAL INFARCT

PATIENT	SEX AND AGE	DURATION OF PAIN PRIOR TO THERAPY	TECHNIQUE FOR BLOCK	NO. OF TREATMENTS	RELIEF OF PAIN	DURATION OF RELIEF
W. T.	M 73	7 hours	Procaine infiltration	1	Complete	2 years (until next infarction)
	M 75	12½ hours	Procaine infiltration	1	Complete	1½ years (to date)
L. Lu.	M 52	23 hours	Ethyl chloride spray	1	Complete	7 months (to date)
I. C.	M 67	21 days	Procaine infiltration	1	Complete	9 months* (to date)
L. Le.	M 46	4 hours	Procaine infiltration and ethyl chloride spray	4	Partial until 7th hospital day, then complete	7 months (to date)

*Precordial chest pain for about two hours during each of two attacks of acute left ventricular failure with pulmonary edema four and six months, respectively, after infarction.

Patients With Effort Angina (Groups 2 and 3).—The difficulties in evaluating any form of treatment in chronic cardiac pain are well known. However, analysis of the results of local block of the somatic component in the eighteen patients of Group 2 with both effort angina and myocardial infarction indicates that this procedure may be effective when the anginal syndrome appears soon after an acute myocardial lesion. Of twelve patients with this type of onset, all received significant relief of both the severity and frequency of anginal attacks, as indicated by increased physical activity and decreased use or discontinuance of nitrites. These patients received an average of about six treatments by local procaine infiltration given at weekly, or occasionally, at biweekly intervals. Ethyl chloride

spray was employed in only one patient; in this patient, numerous trigger areas were present in the skin as well as in the deeper structures. In three of the twelve patients with postinfarction onset of pain, the effort angina was completely abolished by local block therapy even when normal activity was resumed (three, four, and four months of observation after treatment, respectively); effort angina had been present since infarction for four, three, and one and one-half months, respectively. In one case in which anginal pain had been present for as long as ten years since myocardial infarction, marked relief was secured by local infiltration. A long duration of chest pain, therefore, does not preclude a good result in these postinfarction anginal syndromes.

The results in these twelve patients of Group 2, the onset of whose effort angina followed infarction, are to be contrasted with those obtained in the remaining six patients in this group, in whom the anginal syndrome antedated the first myocardial infarct and in whom local block therapy was instituted some time after infarction. In these patients with effort angina of gradual onset, persistent treatment extending even over many months afforded at the best only partial relief, and the anginal syndrome reverted to its previous severity soon after local block therapy was discontinued. These relatively unsatisfactory results are similar to those observed in the nine patients of Group 3 with effort angina of insidious onset, but without acute myocardial infarction.

On the basis of the response to local block therapy, the fifteen patients (six of Group 2 and nine of Group 3) with effort angina of insidious onset appear to represent one class, irrespective of whether infarction occurred intercurrently or not. The therapeutic result in this group is so different from that noted previously in the twelve patients with postinfarction onset of effort angina that various factors have been analyzed to insure that these represent comparable groups. As shown in Table II, the proportion of men was high in both, namely, 87 per cent in the former and 75 per cent in the latter. The average ages were 58 and 59 years, respectively, with almost identical ranges. Marked hypertension was present in 33.3 and 25 per cent, respectively; this difference is not considered statistically significant. In the patients with angina of insidious onset, the duration of anginal pain prior to therapy ranged from four weeks to eight years, as compared with six weeks to ten years in the patients with angina precipitated by infarction. In conclusion, it may be stated that except for the

TABLE II. ANALYSIS OF FACTORS IN EFFORT ANGINA WITH DIFFERENT MODES OF ONSET

ONSET OF PAIN	NUMBER OF PATIENTS	NUMBER OF MEN	AVERAGE AGE (YEARS)	HYPERTENSION		AVERAGE RESPONSE TO LOCAL BLOCK
				NUMBER	PER CENT	
Post infarction	12	9	59 (43-65)	3	25	Good
Gradual	15	13	58 (42-72)	5	33.3	Poor

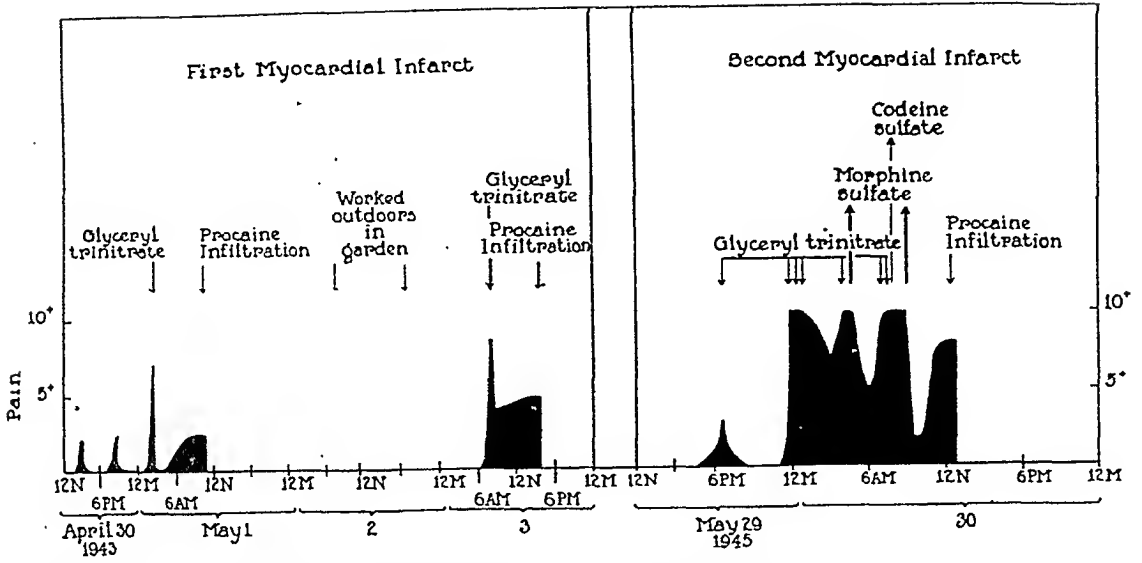


Fig. 1.—Case 1. Influence of medication and of local procaine infiltration on pain for the first and second myocardial infarction two years apart. An arbitrary scale has been adopted to indicate relative intensities of pain.

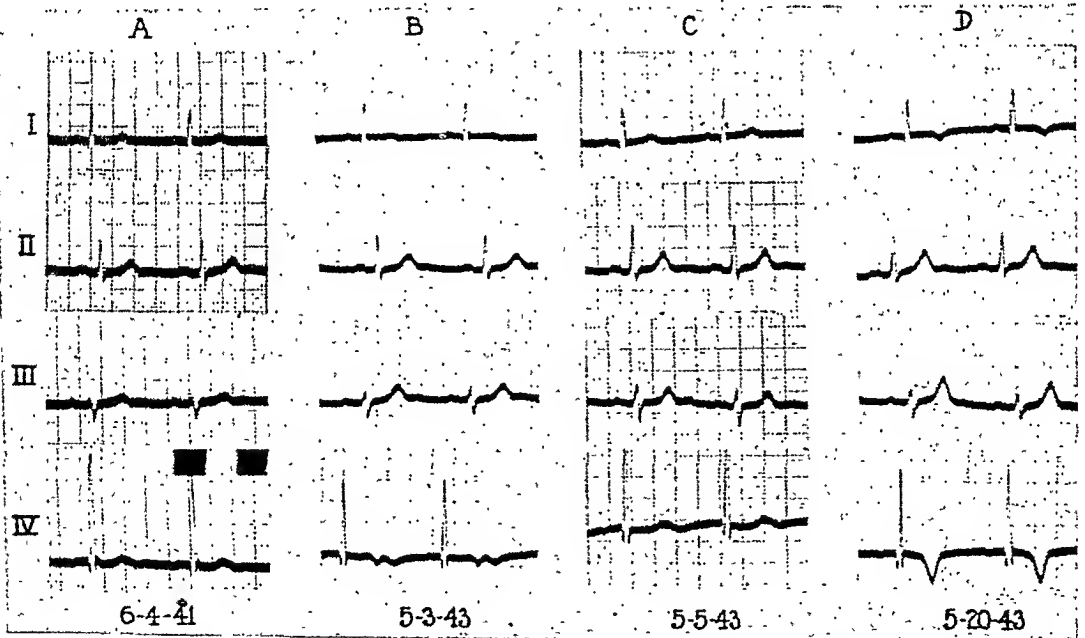


Fig. 2.—Case 1. First infarction. Serial changes of a recent myocardial infarct. A, Routine tracing taken two years prior to the first infarct. Normal record. B, Record taken seven hours after onset of protracted pain and just prior to procaine infiltration. Note abnormal T₁ and T₄. C, Record taken two days after complete relief of pain by procaine infiltration. T₁ and T₄ have now returned to normal. D, Record taken about two weeks later showing change characteristic of an anterior wall infarct.

type of onset of effort angina, no important differences could be discovered in these two groups.

One of the cases with complete relief of anginal pain after local block of the somatic component is reported (Case 3).

ILLUSTRATIVE CASES

CASE 1. *Block by Local Infiltration in Acute Myocardial Infarction.*—

First Myocardial Infarct: On April 30, 1943, when 73 years old, W. T., a white male physician, experienced brief substernal and precordial pain once during the afternoon and once during the evening. This was the first time he had ever had chest pain. During the night he was awakened by a severe attack of substernal pain which radiated to both arms and was partially relieved by a tablet of glyceryl trinitrate, 0.6 mg., placed under the tongue. All the following morning dull pain persisted in the precordium. Because of his extreme discomfort, at 11:00 A.M. (May 1) a number of exquisitely tender spots in the left pectoral muscles were infiltrated with procaine hydrochloride (0.25 per cent solution), and the chest pain ceased immediately. The response of pain to therapy is shown in Fig. 1.

During the preceding years, several acute episodes of pain in the low back, shoulder, and neck had each been promptly relieved by procaine infiltration of the trigger areas in the appropriate skeletal muscles. Because of the previous history of somatic pain and its relief by local injection therapy, the patient disregarded the possibility that the present attack of chest pain might be of cardiac origin, and insisted on continuing his regular activities.

On the following day (May 2), he drove to the country and worked in the garden. The next morning (May 3), he was awakened at 7:00 A.M. by severe substernal pain. One-half hour later, glyceryl trinitrate (0.6 mg.) was followed by appreciable diminution in pain. He remained in bed, but a heavy dull discomfort in the chest persisted during the day. At 2:00 P.M. an electrocardiogram was taken (Fig. 2,B). Seven hours after the onset of protracted pain, several tender spots in the left pectoral muscles were again infiltrated with procaine. This procedure secured immediate and complete relief of pain (Fig. 1).

Examination of the electrocardiogram showed evidence of myocardial damage as compared with the most recent control (Fig. 2,A), but owing to the long interval between these two records, the changes were considered compatible with, but not necessarily conclusive of, a recent myocardial infarct.

On May 4 and 5, the patient reported that he was "feeling fine" and insisted on going to his office. On May 5, a second electrocardiogram (Fig. 2,C) was taken which showed serial changes in the T waves. The blood sedimentation rate was elevated, with a total fall of 32 mm. in one hour. In view of these findings, on May 7, about a week after the initial appearance of precordial pain and four days after the onset of more severe chest and arm pain, the patient was persuaded to accept the diagnosis of acute myocardial infarction, and although he had had no further pain, to remain in bed for a period of six weeks. Later electrocardiograms (Fig. 2,D) confirmed the diagnosis and showed the classical changes of an anterior wall infarct.

The patient remained asymptomatic and made an uneventful recovery, although after the period of bed rest it required several weeks for him to regain his former vigor. There was no recurrence of pain following the second procaine infiltration during the ensuing two years. Follow-up electrocardiograms were normal on several occasions (Fig. 5A).

Second Myocardial Infarct: On May 29, 1945, the patient returned to his home at 5:30 P.M. and complained of substernal discomfort which disappeared after taking a tablet of glyceryl trinitrate (0.6 mg.). Subsequent questioning revealed that for four or five weeks previously he had not been able to lie comfortably on the left side at night because this position induced a vague discomfort in the precordium and sensation of air hunger and constriction of the chest.

On the night of May 29, the patient was awakened at midnight by a most intense substernal pain which radiated down the left arm and which was uninfluenced by repeated doses of glyceryl trinitrate (0.6 mg.) either then or later in the night (Fig. 1). Morphine sulfate (15 mg.) at 4:30

A.M. gave negligible relief, and codeine sulfate (60 mg.) at 8:00 A.M. gave no relief. At 9:15 A.M., the patient received a second dose of morphine sulfate (15 mg.) after which he became moderately comfortable for the first time since midnight. However, relief lasted for only a short while and the pain had returned to its previous intensity before noon. At this time (12:30 P.M.), twelve and one-half hours after the onset of protracted pain, two discrete areas of exquisite tenderness in the left pectoral muscles and one site in the serratus anterior muscle in the axillary region (Fig. 3) were infiltrated with a 0.25 per cent solution of procaine hydrochloride. The second injection was followed at once by the complete disappearance of pain. The restlessness and anxiety vanished simultaneously and the patient remarked that for the first time he felt as if he could take a deep breath. The blood pressure, which ordinarily was about 160/90, at this time was 120/80. The rectal temperature was 97.5° F. (Fig. 4). After the local infiltration, the patient slept most of the afternoon and had no recurrence of pain and no further analgesic medication. A diagnosis of a fresh myocardial infarct was made.

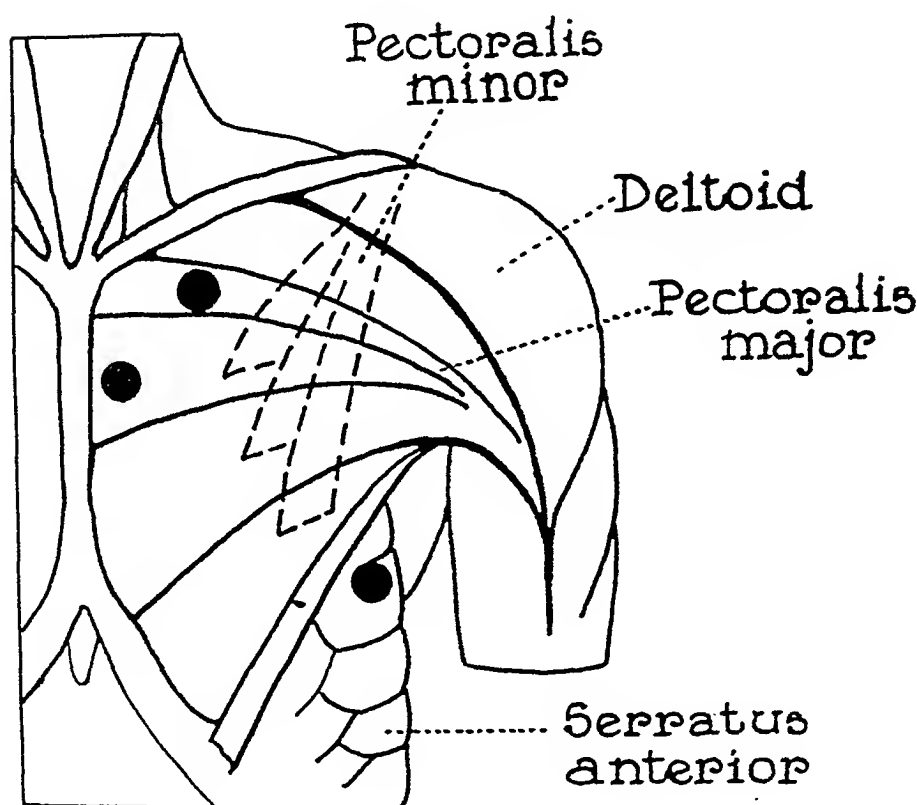


Fig. 3.—Case 1. Second infarction. Dots mark localized areas of deep hyperalgesia discovered in the precordial region following onset of cardiac pain. Procaine infiltration of trigger areas in the muscle at these two sites immediately abolished deep tenderness and also constant chest pain initiated by cardiac lesion.

The clinical course is shown in Fig. 4. At 9:00 A.M. on the following morning (May 31), the rectal temperature had risen to 99.6° F., and the blood pressure had dropped to 95/60. An electrocardiogram (Fig. 5, B) revealed the Q_1T_1 pattern of an anterior wall infarct. At 4:30 P.M. the blood sedimentation rate was 31 mm. at the end of one hour, and the rectal temperature was 102° Fahrenheit. The patient was hospitalized at this time. On admission he did not appear critically ill. The blood pressure was 106/70 and returned gradually to a level of 140/80 at the end of the hospital stay. The temperature returned to normal on the sixth day after the onset. The blood sedimentation rate on the twelfth day of illness had risen to 42 mm. in one hour, and was still elevated on the day of discharge. The white blood cells on the day of admission were 10,700

per c.mm. and returned to normal coincident with the disappearance of fever. Subsequent electrocardiograms (Fig. 5, C and D) confirmed the diagnosis of acute coronary thrombosis with infarction of the anterior wall.

The patient was asymptomatic during the entire hospital stay. Owing to changes in our views regarding bed rest, he was allowed out of bed in about three weeks, and went home four weeks after the onset. At the present time the patient is physically active, and has had no recurrence of pain during the intervening two years. The blood sedimentation rate in November, 1946, was 13 mm. at the end of one hour, and the electrocardiogram was normal.

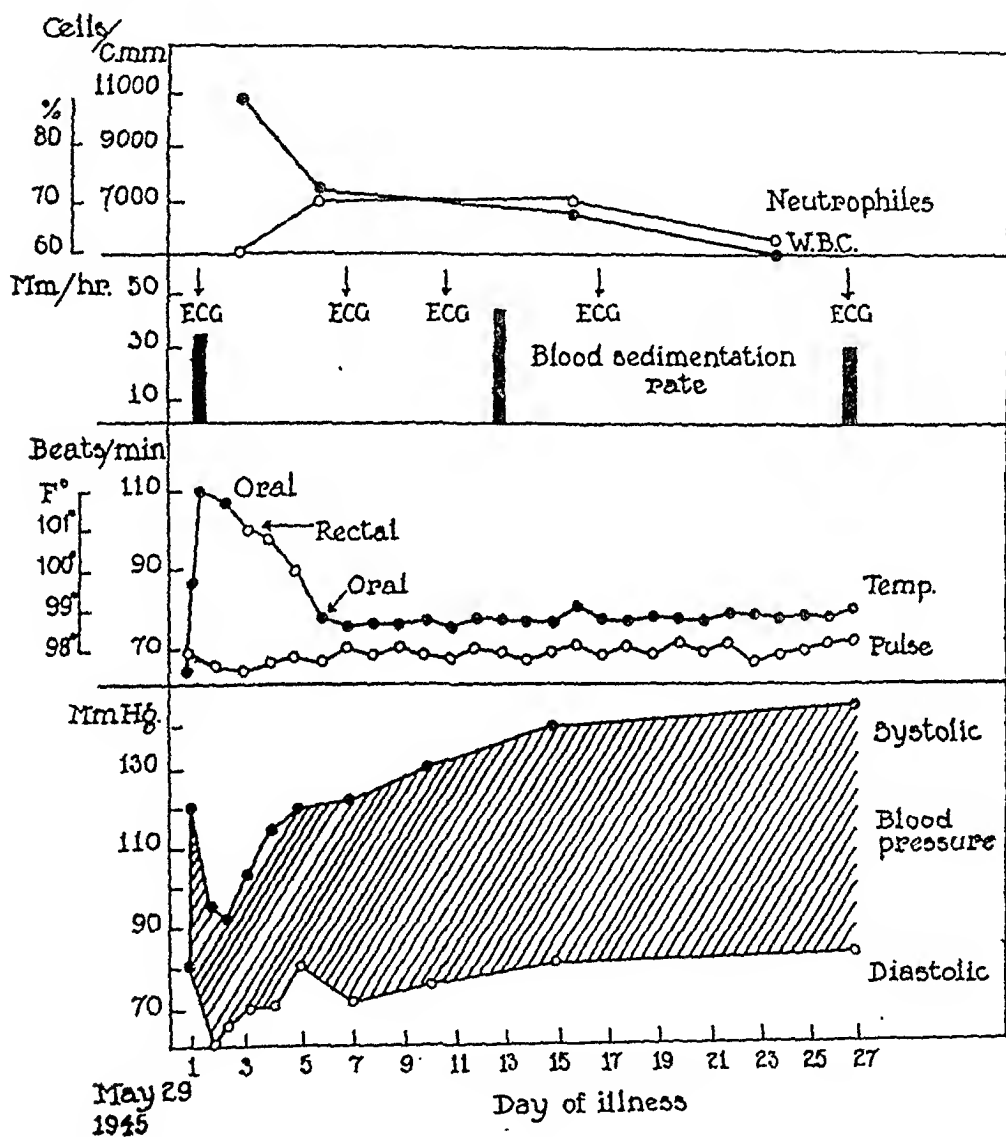


Fig. 4.—Case 1. Second infarction. Clinical course and results of laboratory tests.

Comment: The observations in this case attest the role of the somatic component in cardiac pain. Two separate myocardial infarctions occurred two years apart. The diagnosis each time was substantiated by unequivocal serial changes in the electrocardiogram and by signs of tissue necrosis. Each infarction was accompanied by protracted chest pain which was completely relieved at once by local infiltration of the appropriate areas in the pectoral muscles seven and twelve and one-half hours, respectively, after the onset of cardiac pain. The relief of pain in the first instance lasted until the next infarction, and in the

second instance, has persisted to the present time. Thus, local injection therapy obviated the need for narcotic drugs and simplified the general management of the patient. There is no evidence, however, that such therapy altered the course of the disease.

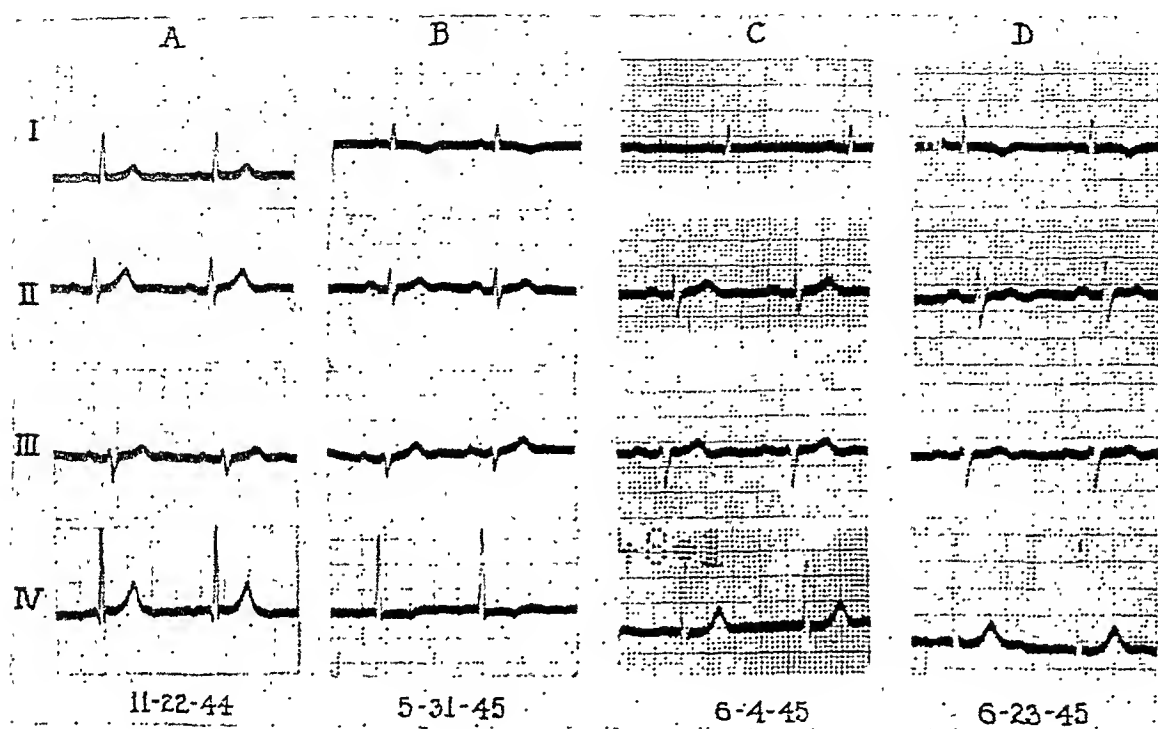


Fig. 5.—Case 1. Second infarction. Serial changes of a fresh myocardial infarct. A, Tracing taken one and one-half years after the first, and six months before the second infarct. Normal record. B, Record taken about forty hours after onset of severe chest pain, and twenty-eight hours after complete relief of pain by procaine infiltration. Note inversion of T_1 and T_4 . C and D, Records taken on the sixth and twenty-sixth days of illness. Note persistence of inverted T_1 , but restoration of T_4 to normal.

In the case of the first infarction, the erroneous assumption was made at first that since local block of the trigger areas in the skeletal muscles abolished pain, the pain must be of somatic origin. It is important to recognize that a visceral etiology of pain cannot be excluded by the fact that pain disappears after local block of trigger areas in somatic structures.

CASE 2. Block by Ethyl Chloride Spray in Acute Myocardial Infarction.—At 3:30 P.M. on Oct. 10, 1946, following an argument with a member of his family, L. Lu., a 52-year-old white male garment worker, had a sudden attack of severe precordial pain which radiated to the left side of the neck, to the left shoulder, and down the arm to the fingers. He was hospitalized at once.

On admission, physical examination revealed an acutely ill man in obvious distress. There was no dyspnea or orthopnea. The neck veins were not distended. The heart was not enlarged. There were no thrills or murmurs. The pulse and ventricular rates were 72 per minute. The blood pressure was 150/90. The lungs were clear. There was no enlargement of the liver or spleen. There was no edema. The temperature on admission was 98.6° Fahrenheit. The blood sedimentation rate was 10 mm. at the end of an hour.

Two electrocardiograms were taken one hour and two and one-half hours after admission, respectively, which showed serial changes (Fig. 6, A and B). In the first record there was depres-

sion of the S-T segments and T waves in Leads I and IV, and in the second, the configuration of these waves had returned to normal.

Because of severe, steady pain, the patient received demerol, 100 mg. every four hours, subcutaneously. When we saw the patient twenty-three hours after the onset of pain, he was still nauseated and complained of constant "squeezing and pressing" pain across the whole sternal and precordial regions and also in the left jaw, neck, and shoulder. Three circumscribed areas of exquisite tenderness to pressure were discovered in the precordial region over the second, fourth, and fifth intercostal spaces, respectively.

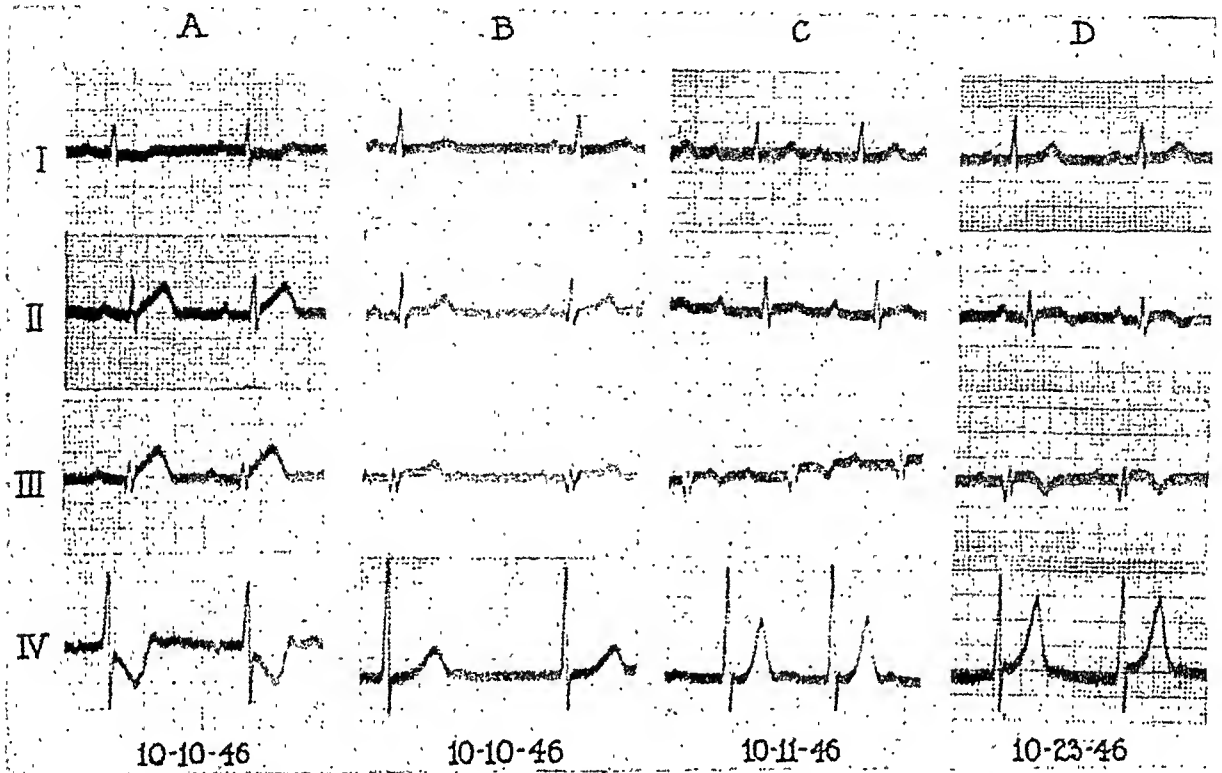


Fig. 6.—Case 2. Serial changes of a recent myocardial infarct. A, Electrocardiogram taken one hour after onset of precordial pain. Note depressed S-T₁ with diphasic T₁; elevated S-T₂ and S-T₃; and depressed S-T₄ with inverted T₄. B, Electrocardiogram taken four hours after first graph. Note appearance of Q₂ and Q₃. T waves in Leads I and IV are now elevated. C, Record taken twenty-three hours after onset of symptoms and immediately after ethyl chloride spray. Note Q₃T₃ pattern indicative of posterior wall infarction. Marked prolongation of A-V conduction is also present. D, Tracing taken thirteen days after onset of symptoms. The P-R interval has returned to normal.

Each of these tender spots was sprayed for from eighteen to twenty-five seconds with ethyl chloride, that is, until blanching or light frosting of the skin occurred. The entire procedure required approximately seven minutes. As the last of the trigger areas was thus blocked, the patient stated that the pain in the chest was completely gone. Within one-half hour, the patient had fallen asleep. Analgesic medication was stopped and no further pain occurred during the hospital stay despite the subsequent appearance of the usual signs of circulatory collapse and tissue necrosis (Fig. 7) which characterize an acute myocardial infarction.

The clinical course is shown in Fig. 7. The blood pressure fell on the second day to 90/50, and rose to 116/70 on the next day; it remained approximately at the latter level until discharge. The temperature rose to 101° F. on the third day, and returned to normal by the fifth day. The sedimentation rose to 85 mm. in one hour on the fifth day, and then gradually dropped to a level of 25 mm. on the eighteenth day. The white blood count, which was 13,000 per c.mm. on the third day, had fallen to normal by the eighth day. Further electrocardiograms revealed the changes characteristic of a posterior wall infarct as seen in the record taken on the fourteenth day (Fig. 6,D).

The patient was discharged from the hospital on the twenty-third day. He was observed for about six months following this infarction. He was hospitalized once because of acute infectious arthritis which responded to salicylates. He has had no recurrence of chest pain referable to the heart.

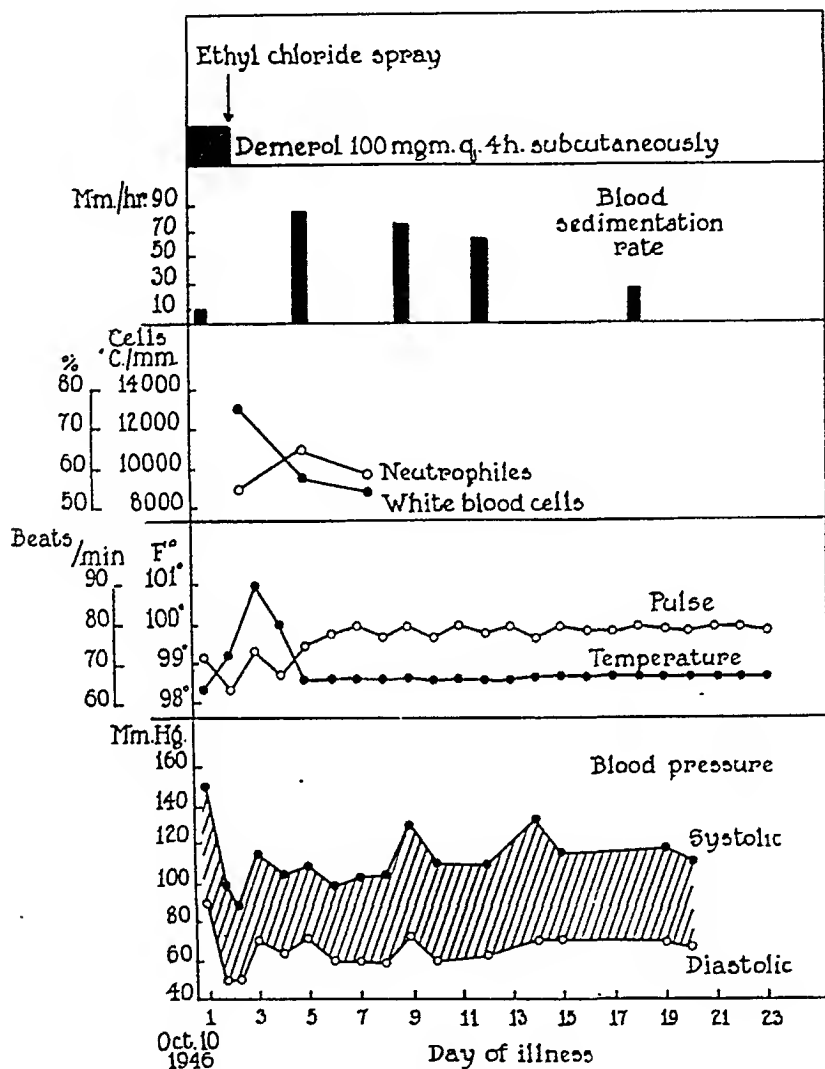


Fig. 7.—Case 2. Clinical course and results of laboratory tests. Note discontinuation of demerol after relief of pain by ethyl chloride spray.

Comment: As in the case of local infiltration of somatic trigger areas, complete and immediate relief of pain initiated by an acute myocardial infarction was obtained in this patient by ethyl chloride spray of the appropriate trigger areas in the precordium. The simplicity of the latter procedure recommends its early trial. However, in those instances in which the trigger areas are located as much as one inch or more beneath the surface of the skin, local injection may have to be substituted for ethyl chloride spray. It should be pointed out that other factors besides the depth of the trigger area, such as the chronicity of pain, may determine the choice of the procedure for local block in a particular case.

As might be expected, the abolition of pain by ethyl chloride spray did not prevent the subsequent appearance of signs of tissue necrosis or serial changes in the electrocardiogram, which establish the diagnosis of a recent infarct.

The prolongation of the P-R interval (Fig. 6,C), which was noted immediately after spraying with ethyl chloride, occurs so frequently as a transitory phenomenon in the course of acute myocardial infarction that in all probability it bears no relation to the use of ethyl chloride spray. An insufficient number of electrocardiograms were taken to answer this question.

The mechanism of action of ethyl chloride spray is not known.⁷ It is interesting, however, that Gammon and Starr¹¹ found that the interrupted application of cold (4 to 10° C.) caused marked diminution of experimentally induced deep muscle pain, and attributed this effect to a poststimulatory depression of the central nervous system.

CASE 3. Effort Angina With Postinfarction Onset.—N. Z., a 54-year-old Italian carpenter, was first seen on June 21, 1945. For about three months he had noticed occasional mild pain in the chest on exertion. About six weeks previously, on May 7 (VE Day), he experienced a severe and protracted attack of chest pain which began after fixing the coal furnace early in the morning. Pain was oppressive across the upper part of the sternum. He put cold towels on his chest and was "very short of breath, but felt all right so long as sitting down." He was not nauseated. The "pressing" pain continued in the sternal and precordial regions all day until the doctor came at 6 or 7 P.M. and gave him "a hypo and some pills." He was told that he had had a heart attack. The patient remained in bed at home for one week. He did not take his temperature. There was no electrocardiogram or other laboratory examination.

During the six weeks following this episode of pain, effort angina was marked. On walking a short distance, pain started around the left costal margin and spread anteriorly over the entire sternum and occasionally across the front of the chest to the right side. It radiated frequently to the left interscapular region and sometimes to the left shoulder and upper arm. The pain came on sooner after effort late in the day than in the morning. There was no nocturnal pain. There was no dyspnea; the patient insisted that it was pain which stopped him from walking and not shortness of breath. There was no cough or edema.

The patient had been unable to work since the "heart attack." The course was apparently stationary; the anginal pain had become neither better nor worse during the six weeks' period.

The patient had been persuaded to give up smoking during this time, although he was always a heavy smoker of cigars. He had also markedly reduced his consumption of alcohol, which had been fairly regular, with intermittent sprees. He was taking no medication, although he had been given some tablets for pain which he preferred not to take because he said that the pain stopped anyway in about five minutes if he rested.

The previous history revealed that the patient had never been subject to "aches and pains" except for occasional mild low back pain. He had always led a very active life with little attention to his health. He had had no serious illnesses and no operations.

On physical examination (June 21), the patient appeared well nourished and muscular. The heart sounds were somewhat distant, with a soft systolic murmur at the apex. The heart did not appear enlarged. The pulse and ventricular rates were 80 per minute; the rhythm was regular. The blood pressure was 135/85. There were no signs of congestive failure. The liver edge was not palpable. The radial arteries were moderately thickened. The oscillometric readings were normal for all four extremities. The reflexes were normal and vibration sense was good in the fingers and toes. Blood Wassermann was negative. Blood sedimentation rate was 30 mm. in one hour. The electrocardiogram (Fig. 8,A) showed changes characteristic of an anterior wall infarct of the myocardium.

Palpation of the muscles revealed localized areas of exquisite tenderness, especially in the left pectoral muscles, but also in other muscles of the left shoulder girdle. There was no specific limitation of motion, although the patient was in general "muscle bound."

At the first visit, a group of trigger areas in the left pectoralis major muscle along the sternal border and two such tender areas located more laterally, probably in the pectoralis minor muscle, were infiltrated with procaine. A total of 20 c.c. of a 0.5 per cent solution of procaine hydrochloride (100 mg.) was used. The insertion of the needle into the myofascial structures at these sites of tenderness set off intense pain reference to the sternum, precordium, front of the shoulder, or interscapular region on the left side. The patient was always able to give a clear description of the spread of pain, which corresponded closely with the predictable reference from the trigger area in question. Tablets of glyceryl trinitrate were given him, but it may be said at this point that he never used them.

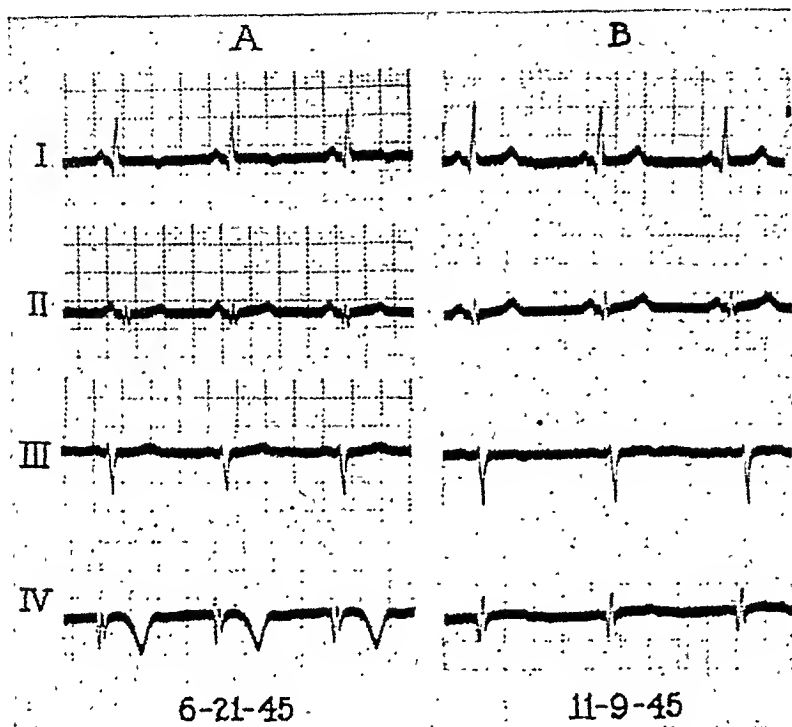


Fig. 8.—Case 3. Serial changes of myocardial infarction. A, Tracing taken about six weeks after acute attack of severe chest pain. Note presence of Q_1 and Q_4 and inversion of T_1 and T_4 . B, Tracing taken five months later, after relief of effort angina by local block of somatic component. Note return of T_1 and T_4 toward normal, but persistence of Q_4 .

At the second visit one week later, the patient reported striking improvement. He had had no pain after walking several blocks, except once when dull precordial pain appeared after walking five blocks; this was not severe and stopped promptly on resting. He had started to work around his house, and prior to coming to the office, made four trips from the cellar to the second floor carrying a window sash each time, without appearance of pain. At this visit, three tender areas in the precordial muscles were infiltrated, and also a larger mass of muscle in the left infraspinatus. When stimulated by the needling, trigger areas in the latter muscle repeatedly set off an intense reference of pain in the shoulder and anterior deltoid region. Twice as much of the procaine solution was used for the second as for the first treatment. No more than this amount was employed at subsequent treatments.

At the third visit, again a week later, the patient said that he could now walk any distance without pain, and that he had returned to work as a carpenter in a wartime shipbuilding plant. He had worked the three preceding nights on the night shift for nine, nine, and seven hours, respectively, without ill effects. His only complaint was that for one day he had had sharp, intermittent pain over the left scapula, apparently unrelated to effort. At this visit, trigger areas were found deep in the left internal rotator muscles of the shoulder (subscapularis and teres major),

which on infiltration set off an intense reference of pain to the region of spontaneous pain over the scapula, as well as along the inner aspect of the upper arm as far as the medial epicondyle of the elbow.

At the fourth visit one week later, the patient reported practically no pain, and he had worked four nights for nine and one-half hours each. His only complaint was of occasional low-grade interscapular pain. Trigger areas were again found in the internal rotator muscles of the left shoulder, and on infiltration the pain reference matched the distribution of spontaneous pain. At this time, little tenderness could be elicited by palpation of the left pectoral muscles in the previous areas of deep hyperalgesia, and on needling the slightly tender spots in the precordium, the pain perceived was negligible and was felt only locally at the site of needling.

At the fifth visit on July 27, after an interval this time of two weeks, the patient said that he had worked seven nights during the first week and six nights during the second, without pain. The work was fairly heavy but he said that he "took it easy and didn't hurry." He complained however of "a light choking feeling in the throat" which began after walking eight blocks with a box of heavy tools on his back and which had persisted off and on ever since. This disagreeable sensation was traced to trigger areas present in the uppermost sections of the pectoralis major muscles on both sides close to the sternum and the clavicles, which set off a reference of pain to the sternum at this level and to the upper part of the trachea. Trigger areas located in the inferior end of the medial heads of the sternomastoid muscles were also infiltrated and induced an upward reference of pain over the sides of the neck.

Subsequently, the patient was seen once a month for five months. He continued to work regularly except when he was "laid off" for a couple of weeks after closing of the war plant on September 10. During this five-month period, he had no real chest pain, in spite of strenuous physical activity which included lifting and carrying lumber. A good part of his carpentry was done outdoors on the exterior of the ships, even in cold and stormy weather. Minor complaints of shifting low-grade pain in the left lower lumbar, left shoulder, right pectoral, and epigastric regions were relieved in each instance by local procaine infiltration of trigger areas in the appropriate muscles, the pain reference from which reproduced the spontaneous pain described. The monthly blood pressure readings were as follows: 142/88, 120/60, 110/60, 110/70, and 150/95. The soft systolic murmur at the apex disappeared. Signs of congestive failure were absent. On November 9, the blood sedimentation rate was 20 mm. in one hour, and the electrocardiogram (Fig. 8,B) had returned essentially to normal except for a deep Q_s. The patient had gained about ten pounds and had not resumed smoking.

The last observation of the patient was on Dec. 6, 1946. At this time, activity was slightly limited in that if he worked hard and at the same time hurried, he occasionally felt a tightness across the upper part of the sternum or in the epigastrium which disappeared promptly on resting. However, this did not bother him enough to keep him from working and did not seem to warrant further treatment.

Comment: In this case, severe effort angina precipitated by an acute myocardial infarct caused total disability from work for a period of six weeks, and showed no tendency toward spontaneous improvement even though the patient had given up smoking and drinking. After this "control" period, the first local block of the most conspicuous trigger areas in the precordial muscles afforded about 90 per cent relief of the anginal pain. Within a few days after the second local infiltration one week later, the patient returned to his previous heavy work in wartime ship construction. During the ensuing five months of observation he continued at his job without loss of time and with freedom from anginal pain, even though he worked outdoors during inclement weather often seven nights per week.

DISCUSSION

Experimentation in animals and human subjects has led to controversy as to whether local anesthetization of the somatic tissues in the area where pain is perceived can block the referred pain induced by direct stimulation of a viscus. A complete analysis of this subject would be out of place in this report since the problem has been recently reviewed.¹² However, it may be pertinent to note that the discrepancies in the literature probably arise at least in part from differences in the character of the stimulus employed, in the nature of the tissue (superficial or deep) infiltrated with procaine, and in the technical difficulties in the way of complete anesthetization of the deeper structures in the area of visceral pain reference. After consideration of such variables and on the basis of their own experiments, Wolff and Hardy¹² conclude: "When pain results from the persistence of primary visceral or other deep noxious stimulation and is associated with [somatic] hyperalgesia, its intensity may be modified by superficial and deep procaine infiltration in the hyperalgesic zones."

Our data suggest that the somatic trigger mechanisms which apparently mediate referred cardiac pain are usually located within the skeletal muscles, although they may reside also in the skin. In the latter instance, cutaneous as well as deep hyperalgesia is present, and a reference of pain may often be elicited by mechanical stimulation of the skin itself. One would expect surface anesthetization to reduce pain only when hyperalgesia of the skin is present, since it has been found¹³ that the effect of procaine infiltrated at the site of hyperalgesia and referred pain (induced by tooth stimulation) is the more dramatic the greater the hyperalgesia and headache previously produced. We have observed, however, that ethyl chloride spray may be effective in relieving referred pain even when no hyperalgesia of the skin is detectable. Although the mechanism of action of this agent in blocking somatic trigger mechanisms is not yet established, the superficial nature of its effects⁷ for the technique employed suggests the possible importance of tactile and other stimuli from the relatively normal skin in the maintenance of the pain cycle. It has been inferred that reinforcement of the effects of noxious stimuli by nonnoxious stimuli takes place within the association areas of the cerebral cortex.¹²

Our observations indicate further that the noxious stimuli from the heart, continuing after acute myocardial infarction, are of such a nature that the pain cycle initiated by this event can usually be blocked at the somatic component. Why this is so can readily be understood in the case of the *constant* pain which may continue for hours or days after such brief trauma to the heart. The conditions may be regarded as analagous to those which exist in joint sprain when pain is immediately and permanently relieved by temporarily blocking the trigger mechanisms established in the periarticular structures, in spite of the persistence of gross signs of trauma.⁷ One may assume that in the postinfarction cardiac pain syndromes, the initial insult to the heart leads to the rapid development of somatic trigger areas within the so-called "reference zone" of the visceral lesion. Soon after the activation of the somatic trigger mechanism, the noxious impulses from the primary source in the heart cease spontaneously, and the con-

tinuation of pain then depends on an autogenic cycle of nerve impulses maintained by the secondary sources in the somatic structures. Blocking the somatic component may be expected permanently to abolish pain when the soma-sensorium pain cycle has become self-sustaining without further dependence on afferent impulses from the heart (Fig. 9, Stage III).

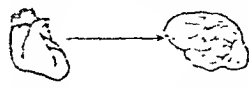
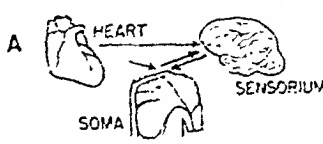
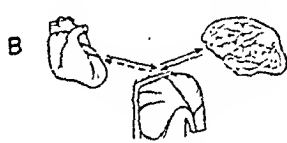
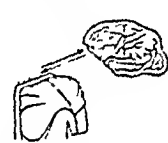
CLINICAL TYPES OBSERVED		EXPLANATION OF CLINICAL DATA	
SOMATIC TRIGGER AREAS	RELIEF BY BLOCKING SOMATIC COMPONENT	THEORETICAL STAGES	SOURCE OF NOXIOUS IMPULSES
ABSENT	—	I. VISCERAL	
PRESENT	NONE OR PARTIAL (DEPEND- ING ON PREDOMINATING PATH- WAY)	II VISCEROSOMATIC	A 
	COMPLETE, BUT TEMPORARY		B 
	COMPLETE AND PERMANENT	III. SOMATIC	

Fig. 9.—Interpretation of results of local block of somatic component in cardiac pain. Stage I represents direct stimulation of sensorium by high intensity stimuli from heart, as in onset of coronary thrombosis or insufficiency. In many patients process ends here without progression to Stages II and III. Stage II represents continuation of process in heart with development of somatic trigger areas continually reactivated by noxious impulses from the heart, as in effort angina. The dotted arrow B suggests that noxious impulses may also travel from somatic trigger areas back to the heart. Stage III represents termination of process responsible for noxious impulses from heart. Somatic trigger mechanisms are now independent and are the sole source of impulses to maintain the pain cycle, as in protracted pain after myocardial infarction.

In the case of the *intermittent* pain (effort angina) precipitated by acute myocardial infarction, it is somewhat harder to understand why blocking the somatic component modifies pain for any length of time, since it is clear that a primary source of noxious impulses is still present in the heart. One would anticipate that, under such circumstances, constant reactivation of somatic trigger mechanisms would occur as the result of the intermittent barrage of fresh impulses from the heart, and that, therefore, block of the secondary sources would produce only temporary or negligible benefit.

One explanation of the good therapeutic results actually observed in this group of cases is based on the concept that spatial summation of cardiac and somatic impulses occurs in the central nervous system.¹⁴ Thus, it is conceivable that when the stimuli initiated in the heart are subthreshold, the sensorium does not register pain unless they are reinforced by stimuli from somatic trigger areas (Fig. 9, Stage II, A). One may postulate further that these subthreshold stimuli from the heart are no longer capable of activating new trigger areas after those initiated by high intensity stimuli at the time of infarction have been removed by local block. That pain impulses may at times travel directly from the heart to

the brain without mediation of somatic structures is suggested by our failure to demonstrate trigger areas in the precordium in some patients with acute myocardial infarction or effort angina (Fig. 9, Stage I).

Another explanation for the protracted relief of postinfarction effort angina by local block therapy is based on the possibility that the somatic trigger mechanisms contribute to the perpetuation of the primary source of pain (Fig. 9, Stage II,B). Although our data provide no evidence that noxious impulses from somatic trigger areas may modify conditions in the heart, the inference that such reflex effects may occur receives support from the work of several investigators. Lindgren¹⁵ showed in acute experiments that anginal pain in subjects with coronary artery disease was reduced or abolished during local anesthetization of precordial structures, as measured by changes in anoxia and exercise tolerance tests; this effect was attributed to improvement in the coronary circulation during local block of somatic impulses. Furthermore, it has been shown that reflex vasoconstriction in localized areas of another visceral system, namely, the brain or spinal cord, may accompany activity of somatic trigger mechanisms, and that localized vasodilatation in the central nervous system may follow local block of the appropriate somatic trigger areas.^{16,17} If comparable relationships apply to the heart, local block of the somatic trigger areas concerned in the reference of cardiac pain would result in release of coronary vasospasm and possibly, therefore, in removal of the primary source of noxious impulses in the heart.

The unsatisfactory response to local block therapy in the group of patients with effort angina due to progressive coronary insufficiency indicates that such intermittent work-ischemia of the heart muscle provides conditions unlike those which exist in postinfarction effort angina. Two possibilities present themselves to explain the relatively poor therapeutic result in angina of gradual onset. It may be that the fresh impulses initiated in the heart with each attack of pain are of an intensity and duration adequate for the continual reactivation of somatic trigger areas (Fig. 9, Stage II,B). Or a preponderance of these fresh impulses may travel directly to the sensorium, so that spatial summation of cardiac and somatic impulses is not essential for the perception of pain (Fig. 9, Stage II,A). In either instance, local block of the somatic trigger areas would be expected to afford negligible or temporary relief of anginal pain.

Our interpretation of the results of local block therapy as presented in the foregoing and as shown schematically in Fig. 9, is in harmony with the categories of referred pain recently formulated by Wolff and Hardy.¹²

It is to be hoped that theoretical considerations regarding neurophysiologic mechanisms will not obscure the clinical value of local block procedures for the symptomatic relief of cardiac pain. The crucial nature of our observations in the subjects with continuing pain after acute myocardial infarction leaves no room for doubt that under suitable conditions cardiac pain may be abolished by local block of the somatic component. Furthermore, the importance of eliminating all possible factors which may induce reflex spasm of collateral coronary arteries is emphasized by experiments which show that interruption of the reflex arc by ablation of the cardiosensory pathways appreciably lowers the mortality

rate following ligation of the coronary arteries in dogs.¹⁸ These findings, together with the observations of Lindgren,¹⁵ undermine the concept occasionally encountered that pain, especially anginal pain, is a protective mechanism to limit the load placed on the myocardium with an inadequate coronary circulation.

SUMMARY AND CONCLUSIONS

1. Observations were made in thirty-one subjects with chest pain due to inadequacy of the coronary circulation, who presented trigger areas in the muscles of the precordium.

2. Local block of the somatic structures concerned in the reference of cardiac pain was carried out either by infiltration of the appropriate trigger areas with a solution of procaine hydrochloride (0.25 to 0.5 per cent in physiologic saline), or by spraying the skin overlying these trigger areas with ethyl chloride.

3. The cardiac pain syndromes which responded to local block of the somatic component were those precipitated by an acute myocardial infarct. This was true for the constant chest pain which failed to subside after infarction (four subjects), and for effort angina which first appeared shortly after infarction (twelve subjects).

4. Unsatisfactory results were obtained by local block in effort angina (fifteen subjects) which either antedated the first infarct or was not accompanied by a known myocardial infarct.

5. The difference in the therapeutic response observed for the two general modes of onset of effort angina was not attributable to differences in age or sex distribution, duration of anginal pain, or incidence of hypertension.

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COMBINED HEPARIN-DICUMAROL THERAPY OF MYOCARDIAL INFARCTION

A CLINICAL AND PATHOLOGIC STUDY

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UNTIL recently, anticoagulants have been used largely in the treatment of venous thrombosis and peripheral arterial occlusion. However, both experimental and clinical evidence has accumulated to indicate that anticoagulants may also have their place in the treatment of coronary thrombosis and myocardial infarction. Solandt and Best¹ demonstrated that heparin could prevent coronary thrombosis experimentally induced in animals. Solandt and associates² also showed experimentally that heparin prevented the development of mural thrombosis over an area of injured cardiac muscle. Dale and Jaques³ have shown that dicumarol prevented venous thrombosis in experimental animals. Recently, Ogura and associates⁴ reported that, following myocardial infarction, there was evidence of increased coagulability of the blood.

The use of anticoagulants for the treatment of myocardial infarction has become of especial interest to clinicians in the hope that certain complications could be averted. The frequent occurrence of mural thrombosis overlying a myocardial infarct and the subsequent occurrence of severe and often fatal emboli have been reported by a number of authors.⁵⁻¹⁰ Recently, Nay and Barnes¹¹ have emphasized the high incidence of embolism occurring during the immediate convalescence from acute myocardial infarction. The work of Peters and co-workers,¹² Nichol and Page,¹³ and Wright¹⁴ seems to indicate that dicumarol is of definite value in preventing emboli following myocardial infarction.

Loewe and Hirsch¹⁵ have shown that heparin will prevent occlusion of collateral veins after traumatic thrombosis of a larger vein. There is a latent period of twenty-four to seventy-two hours before dicumarol becomes effective. During this period, the clot in the coronary artery may extend in a retrograde direction, thus enlarging the area of infarction; therefore, it was thought advisable to administer both heparin and dicumarol initially. When the prothrombin concentration in the blood was reduced to the desired level, heparin* was discontinued.

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In order to evaluate combined heparin-dicumarol therapy, anticoagulant treatment was administered to alternate patients with myocardial infarction; in all other respects, the therapy was identical. This study was begun independently in April, 1946, at the Cincinnati General Hospital and has continued since February, 1947, in collaboration with the "Committee on the Use of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction," of the American Heart Association.

PROCEDURE

Treatment was begun as soon as a definite diagnosis of myocardial infarction could be established, employing the usual clinical, laboratory, and electrocardiographic criteria. All patients were treated within twenty-four hours of the onset of symptoms, except two, who were treated on the second and third day, respectively. Anticoagulant therapy was not begun until an initial prothrombin and clotting time had been determined, using the capillary tube method. The usual initial dose of dicumarol consisted of 200 mg. orally, unless the prothrombin time was prolonged or the patient in severe shock. Simultaneously, 300 mg. of heparin were added to a liter of 5 per cent glucose in water and a continuous intravenous drip was started at the rate of 20 drops per minute. Subsequently, the rate of the drip was regulated in accordance with measurements of the clotting time by the capillary tube method. The clotting time was determined at four-hour intervals, except between 12 midnight and 8 A.M. An attempt was made to maintain the clotting time between 8 to 10 minutes and the rate of the drip was increased or decreased accordingly. The required rate usually averaged between 20 and 25 drops per minute; an occasional patient, however, needed as much as 35 drops per minute. Although the capillary method was only relatively accurate, nevertheless, it seemed that this method was preferable to methods requiring repeated venepunctures.

The prothrombin time was determined approximately twenty-four hours after the initial dose of dicumarol, and daily thereafter until the discontinuance of dicumarol on the twenty-first day. The prothrombin was determined by the method of Quick, using freshly drawn blood and a control plasma for each determination. The results were reported not only as "prothrombin times," but as percentages of normal concentration, using Quick's curve and correcting for each lot of thromboplastin* which was freshly prepared each day.

Heparin was discontinued when the prothrombin concentration fell to 20 to 30 per cent of normal concentration,¹⁶ which usually occurred between twenty-four and thirty-six hours after the first dose of dicumarol. The average patient required between 300 to 400 mg. of heparin during this period. Subsequent dosage of dicumarol was administered only after the daily estimation of prothrombin. The importance of accurate laboratory determinations of the prothrombin concentration should be emphasized.¹⁷ An attempt was made to maintain the prothrombin concentration between 20 per cent and 30 per cent of normal. The daily dosage varied from 0 to 250 milligrams. When the pro-

*Difco Laboratories, Detroit, Mich.

thrombin concentration was above 30 per cent of normal, 100 to 200 mg. of dicumarol was administered; if below 20 per cent of normal, none was given. It should be understood that the dosage of dicumarol varied greatly from patient to patient, and that there was no true "standard dosage." The total dosage of our twenty-five treated patients during the twenty-one-day period of therapy ranged from 800 to 2,200 mg. of dicumarol. A period of twenty-one days was selected for therapy, since previous work had shown that by the twenty-first day after myocardial infarction, the coagulation of the blood was no longer accelerated.⁴

RESULTS

The results are summarized in Tables I, II, and III. All patients tolerated the intravenous drip well. It was noted in many instances that the intensity of the pain and its duration seemed markedly reduced by the intravenous administration of heparin in glucose. No patient receiving heparin therapy suffered pain of longer duration than sixty hours after the institution of treatment; in fact, many were immediately relieved of pain. Since no control observations using glucose alone were carried out, and since the psychologic factors associated with intravenous therapy may have played a role, further observations are necessary before conclusions concerning relief of pain by heparin, per se, can be drawn.

Fifty cases of myocardial infarction have been observed: twenty-five "treated" and twenty-five "untreated" patients. For purpose of brevity, "treated patients" indicates those receiving anticoagulant therapy, and "untreated" those who did not. Five of the treated patients and three of the controls were observed in private hospitals; the others were patients in the Cincinnati General Hospital. It should be emphasized that in the Cincinnati General Hospital private nursing care was not available. The patients were given routine care on a large medical ward. Three of the treated cases and eight of the untreated cases have died. All of the treated cases who died were found to have massive myocardial infarction at necropsy. None showed mural thrombosis or emboli. The case histories and pathologic findings of the three fatal cases who received anticoagulant therapy are appended.

CASE 9.—The patient was a 50-year-old white man. The present illness began on June 10, 1946, with vicelike pain in the chest accompanied by weakness, fainting, and perspiration. Six hours later, when admitted to the ward, the patient appeared acutely ill and in profound shock. The blood pressure when obtainable was 110/80, the pulse was extremely irregular, the rate varying between 32 and 40 per minute. The heart sounds were heard with difficulty. The initial diagnosis was acute myocardial infarction. An electrocardiogram showed complete A-V block with a slow idioventricular rate and classical signs of posterior infarction. Six hours after admission the patient had a convulsive seizure which was followed by syncope. This was thought to be a Stokes-Adams attack.

Heparin, 300 mg., was administered intravenously. After determination of the initial prothrombin time (12.5 seconds), the patient was given 200 mg. of dicumarol. Twenty-four hours later, when the prothrombin time had increased to twenty-one seconds, heparin was discontinued. An additional 100 mg. of dicumarol was given, the total dosage in forty-eight hours being 300 milligrams. On the second hospital day, two additional attacks of Stokes-Adams syncope occurred and the patient excreted only 100 c.c. urine in twenty-four hours. During this period, the heart sounds were barely audible and the pulse was frequently imperceptible. On the third

TABLE I. COMBINED HEPARIN-DICUMAROL THERAPY IN ACUTE MYOCARDIAL INFARCTION

	PATIENTS RECEIVING ANTICOAGULANTS	PATIENTS NOT RECEIVING ANTICOAGULANTS
Number	25	25
Age (mean*)	56.6	58.6
Sex		
Male	88%	72%
Female	12%	28%
Race		
White	92%	84%
Negro	8%	16%
Previous hypertension	60%	44%
Previous heart disease	44%	44%
Previous coronary occlusion	16%	28%
Cardiac enlargement	48%	44%
Diabetes	20%	0
Treatment		
Dicumarol (mg.) mean dosage†	1,421	—
Heparin (mg.) modal	300	—
Digitalis	12%	40%
Complications		
Emboli	4%	24%
Congestive failure	16%	40%
Shock	12%	12%
Hemorrhage	12%	—
Duration of pain after admission (average)‡	18.6 hr.	48 hr.
Died	12%	32%

*Mean Treated

56.6 \pm 1.56 σ = 11.55 years

Diff. = 2 years

Pe diff. = \pm 2.14 yearsDiff. = 2.0 \pm 2.14 years, which is not statistically significant. Therefore both groups are identical as to mean age.

Mean Control

58.6 \pm 1.47

10.91 years

†Calculations based on patients receiving entire course of therapy.

‡Calculations based on patients having severe pain after admission.

hospital day the prothrombin time was 58 seconds, with a control of 14 seconds. By afternoon, two hours before death, it had risen to 120 seconds. One hundred twenty milligrams of vitamin K1 (menadione) were administered without apparent response. The urea nitrogen a few hours before death was 78 mg. per cent. The patient died fifty-two hours after admission.

Autopsy.—The heart weighed 430 grams. The coronary ostia were patent. The trunk and branches of both coronary arteries were tortuous and sclerotic. The right coronary artery was occluded by a thrombus about 4 cm. from orifice of the vessel. The clot measured 1 cm. in length. The epicardium was smooth and contained two pin-point hemorrhages near the apex.

Examination of the myocardium revealed a large area of friable yellow tissue involving the entire length of the posterior portion of the intraventricular septum. The endocardium was intact. The remainder of the myocardium was somewhat brownish in color. The aorta was sclerotic, with numerous dull yellow plaques on the intima. No evidence of gross or microscopic hemorrhage was noted in any organ at autopsy. The brain likewise showed no evidence of hemorrhage.

The pathologic diagnoses were: (1) Far-advanced arteriosclerosis of the coronary arteries with recent occlusion of the right coronary artery by rupture of an atheromatous plaque and subsequent thrombosis. (2) Acute progressive myocardial infarction of the posterior portion of the interventricular septum. (3) Marked chronic passive congestion of the lungs, spleen, and liver with central necrosis in the liver. (4) Possible toxic nephrosis (eighteen hours post mortem). (5) Marked focal fibrosis of the alveolar walls of the lung, possibly from an old pneumonia. Marked chronic passive congestion of the lungs.

CASE 13.—This patient, an 80-year-old white woman, was admitted to the Cincinnati General Hospital on Nov. 14, 1946, and died the next day. The present illness began on the day of admission with a feeling of constriction in the chest and precordial pain with radiation to the right shoulder and back. Her family noticed marked cyanosis of the lips. Two weeks before admission facial weakness and weakness of the right hand developed and persisted to the present admission. A mid thigh amputation of the right leg had been performed three years previously in another hospital for diabetic gangrene. There had been no attempt to control the diabetes during this three-year interval.

After the determination of the prothrombin time (12 seconds), 100 mg. of dicumarol was given by mouth and continuous intravenous administration of heparin was begun. During a twelve-hour period the patient received 200 mg. of heparin. It was noted that the pain, which had been intense on admission, diminished after the heparin was begun and no narcotics were given. One and one-half hours before death, the clotting time was reported as 7.5 minutes (Lee and White). The urine showed 1 plus sugar and 1 plus albumin. While speaking to the nurse, the patient suddenly died twelve hours after admission.

Autopsy: When the breast plate was removed, about 200 c.c. of dark red, clear fluid was found to be present in the left pleural cavity, and about 100 c.c. in the right pleural cavity. A few thin pleural adhesions were present. The blood flowed readily on cutting through the various tissues, and appeared to be more fluid than usual. The pericardial sac measured 15 cm. in its greatest transverse diameter in a chest that measured 30 cm. in its greatest diameter. On incision, dark red blood escaped from the pericardium, as if under pressure. About 150 c.c. of fluid blood were present in the pericardial cavity. In addition, a soft, "current jelly" clot of blood, measuring about 6 mm. in diameter, surrounded the entire heart. It was estimated that between 250 and 300 c.c. of blood were present in the pericardial cavity. The pericardium was lined by smooth and glistening membrane. The thoracic organs were in their normal positions and relationships.

The heart weighed 425 grams. On the epicardial surface of the posterolateral aspect of the left ventricle, about 3 cm. above the apex, there was an erosion measuring 1 cm. in length and 2 mm. in width. This erosion was ragged in appearance. Higher up on the posterolateral aspect of the left ventricle, just below the atrioventricular margin, dark red mottling of the epicardium extended over a diameter of about 3 cm., but there was no erosion in this area. The left circumflex coronary artery was moderately sclerotic but widely patent up to a point about 4 cm. from its origin. At this point, the artery became markedly narrowed for about 2 cm. of its length, and then its lumen again widened out. In the narrowed portion of this artery, where the lumen measured about 2 mm. in diameter, there was found a pink, soft, irregular mass elevated about 1 mm. above the intima. This pink mass occupied about 1 cm. of the length of the artery. On making sagittal sections through the left ventricle, a diffuse, irregular dark mottling of the pink myocardium was observed. This mottling was particularly noticeable between the erosion previously mentioned, at the lower aspect of the ventricle, and the hemorrhagic area in the epicardium previously noted. This mottling appeared to extend in a few places as far as the endocardium. No communication was present between the ragged erosion and the chamber of the left ventricle.

TABLE II. LATENT TYPIC SYMPTOMS

NO.	AGE	SEX	RACE	PREV. HYPER-TENSION	PREV. HEART DIS.	PREV. COR. OCCL.	CARD. EN-LARG.	OTHER DISEASES	TREATMENT			COMPLICATIONS				ECG		DURATION OF PAIN AFTER AD-MISSION	DIED	COMMENTS
									DIGI-MAROL (MG.)	HEPA-RIN (MG.)	DIGI-TALIS	PUL-MONARY EMBOLI	CON-GEST. FAIL.	SHOCK	GROSS HEMOR-RHAGE	ANT.	POST.			
1	59	F	W	+	+	0	+	0	800	300	0	0	0	0	0	+	0	None	0	Doing well 10 mo. after discharge
2	49	M	W	+	0	0	+	0	1100	300	0	0	0	0	0	+	0	48 hr.	0	1st admission
3	49	M	W	+	+	+	+	0	1100	300	0	0	0	0	0	0	+	24 hr.	0	2nd admission, 5 mo. later
4	42	M	W	+	0	0	0	0	1025	300	0	0	0	0	0	+	0	6 hr.	0	Symptom-free, working 4 mo. later
5	47	M	W	0	0	0	0	0	1050	200	0	0	0	0	0	+	0	60 hr.	0	Admitted to private hospital 2 mo. after discharge with second attack
6	45	M	C	+	0	0	0	0	1450	700	0	0	0	0	0	+	0	18 hr.	0	
7	57	M	W	+	0	0	+	0	1575	900	0	0	0	0	0	+	0	18 hr.	0	Angina 27th day of illness; doing well
8	47	M	W	0	0	0	0	Diabetes	1250	300	+	0	+	0	0	+	0	7 hr.	0	Congestive failure 29 days after admis-sion; insulin; doing well
9	50	M	W	0	0	0	+	0	300	300	0	0	+	+	0	0	+	24 hr.	+	Died 48 hr. after admission; pest mortem, seo protocol
10	40	M	W	0	+	0	0	0	800	300	0	+	0	0	0	+	0	48 hr.	0	5th day patient had trans. facial homi-plegia and aphasia which disappeared after 24 hr.
11	62	M	W	0	0	0	0	Perirectal ulcers	1200	300	0	0	0	0	0	+	0	24 hr.	0	
12	55	M	W	+	0	0	0	Asymptomatic syphilis	1500	300	0	0	0	0	0	0	+	6 hr.	0	Doing well on antisyphilitic therapy
13	80	F	W	+	+	0	+	Diabetes	100	200	0	0	0	0	+	0	+	None	+	Death—18 hours; autopsy: incomplete rupture of ventricle
14	68	M	W	0	+	+	+	0	800	600	+	0	+	0	0	+	0	None	0	Died 2 mo. after discharge of congestive failure, pulmonary edema

15	48	M	W	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Doing well; asymptomatic 3 mo. after discharge
16	64	M	C	+	+	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	Doing well; asymptomatic 2 mo. after discharge
17	72	M	W	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Occurred 14th day after spinal fusion operation; doing well
18	67	M	W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Doing well; no symptoms 2 mo. after discharge
19	33	M	W	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	+	Death—15th day; autopsy: large anterior and septal infarct, coronary occlusion, no mural thrombosis or emboli
20	62	M	W	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Developed gross hematuria when prothrombin time fell to 13% of normal; good response with 60 mg. menadione, feeling fine 2 weeks after discharge
21	71	M	W	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Doing well 6 weeks after discharge; developed tarry stool when prothrombin time 17% normal; recovered, no menadione
22	56	M	W	+	+	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0	Patient had attack of severe pericardial pain 10 days before admission; second attack of pain on day of admission
23	61	F	W	+	+	+	+	+	0	0	0	0	0	0	0	0	0	0	0	0	Patient had acute coronary occlusion 3 mo. before present attack; received dicumarol for previous attack in another hospital; is to be kept on dicumarol after discharge
24	50	M	W	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14 hr.
25	74	M	W	+	0	0	+	+	0	0	0	0	0	0	0	0	0	0	0	0	12 hr.
																					Patient confused and disorientated on admission; evidence of diabetic acidosis as well as coronary thrombosis; insulin required throughout

NO.	AGE	SEX	RACE	PREV. HYPER- TEN- SION	PREV. HT. DIS.	PREV. COR. OCCL.	CARD. EN- LARG.	DIGI- TALIS	OTHER DISEASES	COMPLICATIONS				ECG		DURATION OF PAIN AFTER ADMISSION	DIED	COMMENTS
										PUL- MONARY EMBOLI	CONGEST. FAIL- URE	SHOCK	ANT.	POST.				
1	58	F	C	+	+	0	+	+	0	+	0	+	0	0	120 hr.	0		
2	80	F	W	+	+	+	+	0	0	0	0	B.B.B.	+	120 hr.	0			
3	75	M	W	0	0	0	+	0	0	+	0	+	+	Dull entire period	+	Died 18 hr. after admission		
4	59	F	W	+	+	0	+	+	Pneumonia 5 days after admission	0	+	0	+	None	0			
5	69	M	W	+	0	+	0	+	0	+	+	+	+	None	+	Acute pulmonary edema and auricular fibrillation; died 19 days after admission		
6	49	M	W	+	0	0	0	0	0	0	0	+	+	Some dull 240 hr.	0			
7	69	M	W	0	+	0	0	0	Cholecystectomy 1946	0	0	+	+	24 hr.	+	Died 3 days after admission		
8	51	M	W	0	0	0	0	0	0	0	0	0	+	12 hr.	0	Recurrence 2 weeks after discharge; treated at home; angina on effort		
9	41	M	C	+	+	0	+	+	Pneumonia or congestion?	0	+	0	+	Dull 240 hr.	0			
10	46	M	W	0	0	0	0	+	0	+	0	+	0	24 hr.	0			
11	66	F	W	+	0	0	0	0	Pneumonia?	+	0	0	+	None	+	Died 8 days after admission; cause of death, probable pulmonary infarct; no autopsy		
12	79	F	C	0	+	0	+	+	0	+	+	0	+	None	+	Died 8 days after admission; autopsy: septal infarct with pulmonary emboli		
13	55	M	W	0	0	+	0	0	0	0	0	+	+	24 hr.	0	In 2 mo. ago, treated at that time with anticoagulants		

one of the eighty-two patients in Class I and Class II* had congestive heart failure, whereas seventeen of the forty-nine patients in Class III and Class IV presented this complication (Table VI).

TABLE IV. EFFECT OF DURATION OF DISEASE ON HEART FAILURE

DURATION IN YEARS	TOTAL PATIENTS IN GROUP	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
0-9	26	25	1	4
10-14	32	28	4	13
15-19	32	26	6	18
20 and over	13	10	3	23
Average duration	—	12.0 years	17.0 years	—
Duration unknown*	28	24	4	14

*Patients who did not know they had heart disease until coming to clinic or without a history of previous rheumatic manifestations.

TABLE V. EFFECT OF AGE ON HEART FAILURE

AGE GROUPS IN YEARS	TOTAL	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Under 20	20	18	2	10
20-29	78	69	9	12
30-39	29	23	6	20
40 and over	4	3	1	25
Average age	—	24.3	27.8	—

A history of previous failure was likewise found to be significant. Every patient who decompensated during a previous pregnancy did so again during the observed pregnancy. However, 9 per cent of those who had never had failure before developed it during the observed pregnancy (Table VII).

It has been stated that when the aortic valve is damaged the patient faces a greater risk during pregnancy than when the mitral valve alone is involved.^{15,28,39} Our experience does not confirm this observation. Table VIII shows that failure

*The classification of the New York Heart Association was used:⁵

Class I: Patients with cardiac disease and no limitation of physical activity;

Class II (formerly 2a): Patients with cardiac disease and slight limitation of physical activity;

Class III (formerly 2b): Patients with cardiac disease and marked limitation of physical activity;

Class IV: Patients with cardiac disease and who are unable to carry on any physical activity without discomfort.

A probe introduced into the upper part of the myocardium at the posterolateral aspect of the left ventricle passed easily from the middle of the myocardium, emerging at the previously mentioned erosion in the epicardium near the apex. The first sagittal cut, made midway between the erosion and the upper portion of the left ventricle, revealed about 5 c.c. of moderately congealed dark red blood trapped in the interstices of the myocardial wall. Moderate sclerosis was present in the other coronary arteries, and there was some narrowing of the left descending coronary artery about 6 cm. from its origin, but no other thrombi were present.

Anatomic Diagnosis.—

Gross: Coronary sclerosis, thrombosis of the left circumflex coronary artery, acute myocardial infarction of the posterior and lateral aspects of the left ventricle, and incomplete rupture of the ventricle into the pericardial sac, with hemopericardium and cardiac tamponade.

Microscopic: (1) Advanced atherosclerosis of coronary arteries with recent rupture of an atheromatous plaque in the circumflex artery, and acute coronary thrombosis. Early fibroblastic activity at point of attachment and beginning endothelial proliferation would suggest the age of the thrombus to be about two to six days. No conclusive evidence of extension proximally was seen, since no fibroblastic activity was seen in thrombus 4 mm. proximal to point of occlusion. (2) Extensive myocardial infarction, with marked neutrophilic reaction and early focal fibroblastic activity (age, about two to six days). Several small, fresher infarcts, without reaction at edges of larger infarct, were observed. The largest one extended from the endocardium to the epicardium in the apical half of ventricle. (3) Extensive hemorrhage into the large infarct, with evidence of some continuity with circulating blood, since there was thrombus formation in some of the hemorrhagic masses in the myocardium, of a type which forms only in circulating blood.

CASE 19.—A 33-year-old man entered the hospital on Dec. 20, 1946, complaining of precordial pain. About two months before entry, the patient noted dull aching pain in the precordial region, brought on by exertion. This distress progressed gradually, and one month later, became relatively constant in character, with radiation to both sides of the neck, shoulders, arms, and occasionally to the back; the pain was aggravated by deep breathing. The patient walked about at night to relieve the pain, without much success. For about three years the patient was known to have had moderate hypertension and tachycardia. There was occasional palpitation, but no dyspnea. In 1938, a thyroidectomy for thyrotoxicosis was performed.

Physical examination revealed the patient to be well developed and obese, and lying quietly in bed. The heart did not appear to be enlarged; the rhythm was regular; the rate, 132; the blood pressure, 120/95; and the second pulmonic greater than the second aortic sound. The heart sounds were distant. The remainder of the examination was essentially negative. An electrocardiogram showed sinus tachycardia with sagging S-T₁ and S-T₂ and flattened T waves. An x-ray film of the chest showed cardiac enlargement. On the day following entry, the patient had an acute attack of precordial distress and presented manifestations of shock, although the blood pressure was 132/94. Subsequently, he was treated with sedation, heparin, and dicumarol. With the exception of a rise in temperature following this attack, the course thereafter appeared satisfactory, and the prothrombin time was adequately elevated. At about 2 A.M. on January 5, the patient developed dyspnea and thereafter rapidly became comatose. He died at 3:25 A.M. Jan. 5, 1947.

Autopsy: The serous surfaces of the pericardium were smooth and glistening, but the sac contained approximately 120 c.c. of turbid yellowish fluid. The heart weighed 470 grams. There was moderate dilatation of the right ventricle and an area of apparent softening over the left apical region. On section, a post-mortem clot was noted in both chambers. The right ventricle measured 3 mm. in thickness and the left ranged from 16 mm. at the base to 2 mm. at the apex. The thinned portion of the apex of the left ventricle, for a distance of 4 cm., was discolored by reddish brown to bright yellow necrosis, and this process extended to the lower half of the interventricular septum, over an area measuring 5 centimeters. These changes were obviously due to myocardial infarction. Elsewhere, the muscle was firm and beefy red. No mural thrombus

was noted. The main branch of the left coronary artery, at a point 1.5 cm. from its origin at the level of its bifurcation into the circumflex and descending branches, showed occlusion by a firm grayish brown fixed thrombus, which obtruded upon the orifice of the circumflex branch and continued into the descending branch for a distance of 2 centimeters. Beyond this point, at which some calcification was noted, atheroma was slight in degree and the vessel lumina were patent. The right coronary was not remarkable.

DISCUSSION

An exact comparison between the "treated" and the control group cannot be made, since autopsies were obtained in only three of the eight control patients who died. Of the controls, the patient in Case 12 showed septal infarction, mural thrombosis, and multiple pulmonary emboli. The patient in Case 18 showed old infarction involving the left apex of the heart, and a recent infarct involving the posterior portion of the left ventricle as well as the intraventricular septum. Overlying the septal infarct was a large mural thrombus. The patient in Case 25 showed infarction of the intraventricular septum, thrombosis of the right auricular appendage, pulmonary emboli, and multiple small pulmonary infarcts. Of the five remaining cases, one died in shock sixty-eight hours after admission, the second probably died of pulmonary infarction on the eighth day. The third died of shock eighteen hours after admission, and the fourth died of classical symptoms of pulmonary infarction on the nineteenth hospital day, while apparently improving. The fifth patient, who had persistent dyspnea throughout his illness, died suddenly on the twenty-eighth day. An autopsy was not obtained in this case.

From Table I, it would seem that only one (Case 10) of the treated patients developed any signs suggestive of embolic phenomena (transient facial palsy and aphasia lasting twenty-four hours). These signs were noted when the prothrombin concentration was not sufficiently depressed. This patient's complete recovery and the brevity of symptoms suggested vasospasm rather than embolism as the cause of the neurological signs. Embolic phenomena occurred in six of the untreated patients in from two to nineteen days after the onset of coronary thrombosis.

Three of the treated patients showed evidence of hemorrhage. One patient (Case 13), who died eighteen hours after admission, was found to have rupture of the epicardial surface of the heart with 200 c.c. of blood in the pericardium. It is doubtful, however, that this rupture was due to the anticoagulant therapy, for the patient had received heparin for only twelve hours, and the clotting time one-half hour before death was only 7.5 minutes by the Lee-White method. The prothrombin time at the initiation of treatment (100 mg. dicumarol) was 12 seconds, with a control of 12 seconds.

Another patient (Case 20) developed gross hematuria when the prothrombin concentration fell to 13 per cent of normal. Red blood cells disappeared from the urine after the administration of 60 mg. of menadione intravenously. The patient in Case 21 showed one tarry stool when the prothrombin concentration fell to 17 per cent of normal. The patient was given no specific therapy, and no further evidence of hemorrhage was noted.

All patients have been followed in the Outpatient Dispensary of the Cincinnati General Hospital, the longest follow-up being one year and the shortest, one month. There have been recurrent myocardial infarctions in three of the treated and in one of the untreated patients. In the treated patients, the infarcts recurred two months, three months, and five months, respectively, after the patients' discharge from the hospital. In the untreated patient, the new infarct occurred two weeks after hospital discharge.

SUMMARY AND CONCLUSIONS

1. Combined heparin-dicumarol therapy has been used in twenty-five cases of acute myocardial infarction: twenty in the Cincinnati General Hospital and five in private hospitals.

2. The control group of twenty-five patients was obtained by omitting anticoagulants in every other patient with myocardial infarction admitted to the hospital. Supportive treatment was identical in the treated and untreated cases.

3. Although the series of cases is too small, and the variables of the disease itself too wide to make statistical analysis significant, it appears that the use of heparin-dicumarol adds no additional hazard to the treatment of acute myocardial infarction.

4. There were eight deaths in the control series of twenty-five cases (32 per cent) and three deaths in the series of twenty-five cases (12 per cent) treated with anticoagulants.

5. Autopsies were performed on the three treated cases who died. Neither mural thrombosis nor embolism was present, although two of the patients died within forty-eight hours after the onset of symptoms. One patient showed incomplete rupture of the ventricle with hemorrhage into the pericardium.

6. Emboli occurred in six of the twenty-five cases in the control series (24 per cent), and possibly in one of the twenty-five cases treated with anticoagulants (4 per cent).

ADDENDUM

Since this manuscript was submitted, nineteen additional patients have been treated with anticoagulants and nineteen controls have been observed. Thus, forty-four patients have received anticoagulants and forty-four have served as controls. The mortality in the untreated group was 45 per cent; in the patients treated with anticoagulants, 20 per cent. In the control group, thromboembolic complications occurred in 27 per cent; in the group receiving anticoagulants, in 7 per cent.

Dr. Pearl Zeek performed the autopsies on Cases 9 and 13, and Dr. Edward Gall on Case 19.

Dr. T. J. LeBlanc, Professor of Preventive Medicine, College of Medicine, University of Cincinnati, helped in the preparation of the tables.

Miss Lois Ames and Miss Jean Noertker gave technical assistance.

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THE DETERMINATION OF THE PROGNOSIS OF PREGNANCY IN RHEUMATIC HEART DISEASE

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THE opportunity to observe the clinical behavior of women with rheumatic heart disease who go through pregnancy made it possible for us to examine and evaluate the criteria recommended for selecting the good from the poor risks. One of the earliest studies in this field was made in 1878 by MacDonald¹ who, on the basis of thirteen of his own cases and the reports of eighteen cases by others, emphasized valvular defects and certain specified symptoms as important guides to prognosis. Much progress has since been made in establishing more dependable aids, and it is of interest that MacDonald's pessimism, understandable in the face of a 55 per cent mortality, has to a large extent disappeared. Credit for much of the advance made toward clearer thinking and sounder clinical judgment belongs to James Mackenzie, who approached the problem from the point of view of cardiac functional capacity. In 1921 he wrote,² "Estimation of the significance of murmurs, as of all other signs, should be based not on the murmur itself, but on the functional efficiency of the heart When ten or fifteen years after the causative rheumatic attack . . . the response to effort is good, then the outlook is favorable When there is marked inefficiency of the heart, shown by breathlessness on slight exertion, rapid pulse, or easily excited palpitation, then there is danger in pregnancy."

Most of the papers in the past twenty-five years support, amplify, or translate into more specific terms Mackenzie's basic rules; none question their validity. In general, the criteria for prognosis as advocated by most authors may be grouped as follows: (1) The amount and degree of structural damage to the heart; (2) the functional capacity of the heart; (3) arbitrary factors, such as age, history of previous failure, and auricular fibrillation.

Not all observers are in agreement as to the relative significance of each of these clinical features. Indeed, several presumably conflicting opinions seem to exist. (These considerations will be taken up in the discussion.) In our experience many of the enumerated signs were found to be very useful, others less so. But it became clearer as our observations accumulated that when these various and apparently unrelated criteria were considered as part of a more inclusive factor, they attained increased meaning and usefulness. This factor

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lies in determining where in the course of the natural history of rheumatic heart disease the individual patient belongs, and this has become the basic principle by which we make our decision. From this, one may prognosticate what the subsequent course is likely to be. Allowance has to be made for the additional work to be done by the heart during the second half of pregnancy. In primiparous women this increment may be difficult to gauge by clinical means, but in multiparous women the previous pregnancy usually constitutes a functional test of the capacity of the heart to do this extra amount of work.

In utilizing this principle one presupposes a familiarity with the course of rheumatic heart disease. Such knowledge is available and has been admirably presented by Cohn and Lingg^{3 a, b} of the Research Committee of the New York Heart Association. This will be discussed more fully in the latter part of the paper. One also presupposes, and this is of fundamental importance, that pregnancy itself does not alter the natural history of the disease. This we believe to be true and we will present evidence to support such a contention. We also believe that it has not been demonstrated that one or more pregnancies, if completed uneventfully, shorten the life of the patient.

In determining prognosis according to the position of the patient in the course of her rheumatic heart disease, some degree of uncertainty will, of course, limit the physician's prediction. He is, after all, applying a general rule based upon observations on many thousands of patients to a single individual. But the magnitude of error inherent in this method we will show to be no greater than in the others. There are, on the other hand, several advantages to recommend it. It lends rationale to rules which heretofore seemed arbitrary. For example, auricular fibrillation, universally accepted as an unfavorable sign, is of grave prognosis not because the arrhythmia per se is hazardous, nor because it presents therapeutic difficulties, but because, as has been pointed out by DeGraff and Lingg,⁴ it indicates that the patient has reached an advanced stage in her disease. Another example is the history of heart failure in the past, which has a similar implication as will be seen later. This method of determining prognosis also gives a cohesiveness to the several unrelated rules previously used and simplifies them in a manner which facilitates clinical application. Finally, it enables the physician to predict several years in advance, as he is often asked to do when consulted premaritally, whether or not pregnancy will be reasonably safe at a given time in the future. It should be added that a recrudescence of rheumatic fever may alter and accelerate the course of the illness and thus invalidate an opinion based on the assumption that the heart disease would remain inactive. This would constitute a serious limitation were it not true that exacerbations of rheumatic fever are rare during the childbearing period.

This paper is essentially an exposition of this basic principle of determining prognosis of pregnancy not by several arbitrary rules or physical signs alone, but by establishing what position the individual patient occupies in the natural course of rheumatic heart disease.

CLINICAL MATERIAL

A prenatal cardiac clinic was established at Bellevue Hospital in 1939, and has been conducted jointly by the Departments of Medicine and Obstetrics of the Third (New York University) Division. Sessions were held in the general prenatal clinic, making it convenient for the patient to be seen by the obstetrician and the cardiologist during the same visit.

Each patient included in this series was examined and studied by the authors.* The interval between visits varied from one week to one month, depending on the period of gestation and the cardiac status. Special attention was given to the history of rheumatic fever and, when possible, reports were obtained from other hospitals and clinics concerning the patient's previous rheumatic manifestations and the course of her heart disease. In addition to the data on weight, height, blood pressure, hemoglobin, urinalysis, and Wassermann test, the vital capacity under uniform basal conditions was also determined at each visit. Teleroentgenograms and electrocardiograms were taken of the patients in the early and late ante-partum and again during the post-partum period. In cases where the diagnosis was in doubt a stethogram and esophogram were used as diagnostic aids. The final cardiac diagnosis was made by the same observer (J.J.B.) in conformity with the criteria set by the New York Heart Association.⁵ This observer studied the course of adult rheumatic cardiac patients in one of the member-clinics of the New York Heart Association for many years.

From October, 1939, to July, 1945, 131 women were observed through pregnancy and puerperium. In eleven other cases pregnancy was interrupted because the prognosis was considered unfavorable.† In each of these cases sterilization was urged, for it was felt that one who was already a poor risk would be unlikely to improve as her heart disease advanced.

The 131 patients were delivered of 133 babies. These included four mothers who gave birth to twins and two mothers who died undelivered. There were eighty-three spontaneous deliveries, thirty-nine forceps, and eight breech deliveries. Cesarean section was performed on three patients for strictly obstetrical reasons. We could see no indication to recommend this procedure on a cardiac basis.‡

OBSERVATIONS

Maternal Mortality.—Table I lists the maternal mortality rate from rheumatic heart disease reported in the literature from 1936 to 1946, inclusive. Re-

*A number of patients failed to attend the ante-partum clinic and were seen by us for the first time at term on the obstetrical wards. No patient with rheumatic heart disease delivered on our obstetrical service was excluded from this series.

†During the four years preceding the period of this study, from 1935 to 1939, thirty abortions were done for patients with rheumatic heart disease.

‡The presence of rheumatic heart disease, per se, is no longer acceptable as an indication for cesarean section. It may occasionally be resorted to as a means of terminating prolonged labor in order to reduce the danger of heart failure. Authors reporting their own results in groups of patients where cesarean sections were done frequently as compared with those where it was done infrequently agree that the fatality rate is higher in the former group.^{6,7} This may be attributed in part to the fact that the greater risks were more likely to undergo section. It is, therefore, important to note that among patients with heart disease of equal severity (Classes 3 and 4) the death rate is significantly higher in the group delivered abdominally (hysterotomy or cesarean section) than vaginally.⁸

ports prior to 1936 were not included since they have been collected and published by Jensen.^{28, p.128} Those after 1936 show a striking reduction in mortality rates; from 9.38 per cent for the period between 1890 to 1922 to 3.24 per cent from 1936 to 1946. This advance is very likely a result of better understanding

TABLE 1. REPORTED DEATHS AMONG PREGNANT WOMEN WITH RHEUMATIC HEART DISEASE (1936 TO 1946)

AUTHORS	YEAR	NO. OF PATIENTS	NO. OF DEATHS	PER CENT DEATHS
Hay ⁹	1936	66	1	1.5
Henderson ¹⁰	1936	76	2	2.6
Hagedorn ¹¹	1937	50	5	10.0
Harris ^{12*}	1937	100	8	8.0
Lamb ¹³	1937	102	7	6.9
McClure ¹⁴	1937	69	3	4.3
Naish ¹⁵	1937	427	11	2.6
Pardee ^{16†}	1937	50	1	2.0
Carr ¹⁷	1938	44	1	2.3
Turino and Antony ¹⁸	1938	102	6	5.9
Lange ¹⁹	1939	322	6	1.9
Clahr, Klein, and Greenstein ²⁰	1940	181	4	2.2
Jensen, Wegner, Keys, and Smith ²¹	1940	108	8	7.4
Gorenberg and McGleary ^{22‡}	1941	345	10	2.9
Hamilton and Thomson ⁶	1941	781	37	4.7
Bramwell and Longson ²³	1942	312	22	7.1
Brown and Sage ⁷	1942	32	1	3.1
Gorenberg ²⁴	1943	223	8	3.6
Jones ²⁵	1943	74	4	5.4
Sampson ²⁶	1943	60	0	0.0
Mendelson ⁸	1944	1,089	8	0.7
Scott ²⁷	1944	114	3	2.6
Bunim and Rubricius	1947	142	2	1.4
Total		4,869	158	3.24

*Only deaths occurring within thirty days post partum were included in this table.

†Three additional deaths occurred after discharge from hospital from subacute bacterial endocarditis, coronary thrombosis, and "unspecified cause," respectively.

‡The authors state that 95 per cent of the patients had rheumatic heart disease.

of heart disease and its treatment, more skillful and conservative obstetrical management, a closer cooperation between the obstetrician and the internist, and the advent of chemotherapy. Some reports from abroad have not been included because they are still unavailable in this country. Other reports, both foreign and American,²⁹⁻³⁸ could not be included because the authors did not specify the type of heart disease present either among the total number of patients or among those that died, or both. It should not be assumed that all deaths listed were from rheumatic heart disease, since many writers made no distinction between the deaths resulting from the heart disease and those due to causes unrelated to it.

As will be noted, in our group there were two maternal deaths. One of our patients, 20 years of age, died of a staphylococcic bacteremia during the fifth month of her first pregnancy. There was no discoverable focus of infection. The other patient, 33 years of age, died of heart failure in the ninth month of her seventh pregnancy. This patient was first seen by us at the end of her sixth pregnancy. At this time she manifested symptoms of diminished cardiac reserve and sterilization was therefore advised. The patient did not consent to this procedure, left the hospital, and did not report for post-partum care. She reappeared during the twenty-seventh week of her next (seventh) pregnancy and was then in congestive failure. Immediate hospitalization was urged in vain. The next day she was admitted in pulmonary edema. After several days of intensive treatment her condition improved. She was advised to remain in the hospital until term but she refused to do so. Several weeks later, the physician who had attended her at home reported that she died undelivered.

Infant Mortality.—The infants delivered on the obstetrical service of Bellevue Hospital during the period of our study were classified for the purpose of this analysis into three groups: infants of mothers with normal hearts, infants of mothers with rheumatic heart disease without failure, and infants of mothers with rheumatic heart disease with failure (Table II and Fig. 1). The mortality rate for infants of mothers with compensated heart disease was not significantly higher than for infants of normal mothers. The mortality rate for infants of mothers with congestive heart failure, however, was 30 per cent, whereas in the compensated group it was 9 per cent and in those with normal hearts, 7 per cent. This difference seems striking, although the number of patients with failure was only eighteen; larger groups would have to be analyzed to establish its significance. Actually, the difference and the standard error between the compensated and decompensated groups just falls short of being statistically significant (21 ± 11.1).

Congestive Heart Failure.—Eighteen of the 131 patients developed congestive failure during pregnancy, an incidence of 14 per cent.* Failure occurred most frequently during the second half of pregnancy (Table III). It should be noted that more instances of failure occurred in the last lunar month than in any preceding month.

*The criteria for congestive failure were pulmonary edema, paroxysmal nocturnal dyspnea, basal rales, or a palpable, tender liver.

TABLE II. EFFECT OF HEART FAILURE ON INFANT MORTALITY: PERCENTAGE DISTRIBUTION

	INFANTS DELIVERED OF NORMAL MOTHERS OCT. 1939 TO OCT. 1943		INFANTS DELIVERED OF MOTHERS WITH HEART DISEASE BUT NOT IN FAILURE		INFANTS DELIVERED OF MOTHERS IN HEART FAILURE	
	NO. INFANTS	PER CENT	NO. INFANTS	PER CENT	NO. INFANTS	PER CENT
Total number of infants delivered	6,263	100	115	100	18	100
Born at term alive and well	5,452	87	97	84	12	66
Premature births alive and well*	392	6	8	7	1	6
Stillbirths, viable	129	2	3	3	2	12
Stillbirths, nonviable†	174	3	5	4	1	6
Neonatal deaths‡	116	2	2	3	2	12

*Infants whose birth wt. was 5 lbs. or less were considered premature.

†Infants weighing less than 3 lbs. were classified as nonviable.

‡Neonatal deaths included babies who died within forty-eight hours after birth.

TABLE III. EFFECT OF ADVANCING PREGNANCY ON HEART FAILURE

WEEKS OF GESTATION	NUMBER OF PATIENTS IN FAILURE
1- 4	0
5- 8	0
9-12	0
13-16	0
17-20	3
21-24	1
25-28	3
29-32	2
33-36	3
37-40	5
Post partum	1

The expected date of delivery was taken as the end of fortieth week of gestation.

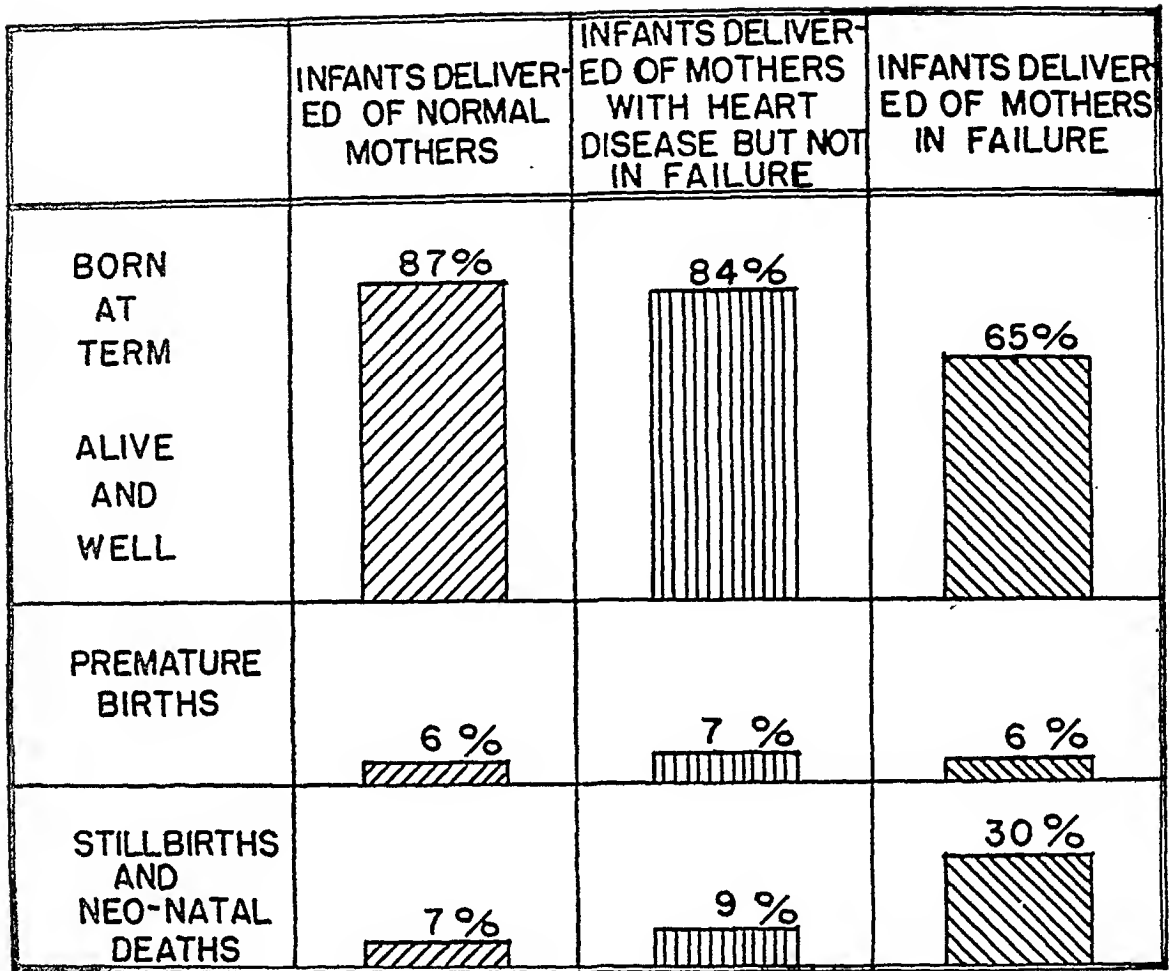


Fig. 1.—Effect of heart failure on infant mortality, percentage distribution.

The interval of time from the onset of the first rheumatic manifestation to the observed pregnancy was determined in 103 patients (Table IV).^{*} As the interval lengthened, the incidence of failure increased. Of those who had had rheumatic fever for less than ten years, 4 per cent went into failure; whereas, of those who had had it longer than fifteen years, 18 per cent or more became decompensated. Patients who failed had heart disease for an average duration of seventeen years, five years longer than those who did not fail. The average age of the group in failure was 27.8 years; of the other group, 24.3 years (Table V). Our data show that about one-fourth of the patients above the age of 30 years, or those who had had rheumatic fever for more than twenty years, developed congestive failure during pregnancy.

A close relationship was observed between the limits of cardiac reserve that existed before pregnancy and the incidence of failure during pregnancy. Only

^{*}In the other cases, there was either no initial episode or the patient did not remember it.

one of the eighty-two patients in Class I and Class II* had congestive heart failure, whereas seventeen of the forty-nine patients in Class III and Class IV presented this complication (Table VI).

TABLE IV. EFFECT OF DURATION OF DISEASE ON HEART FAILURE

DURATION IN YEARS	TOTAL PATIENTS IN GROUP	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
0- 9	26	25	1	4
10-14	32	28	4	13
15-19	32	26	6	18
20 and over	13	10	3	23
Average duration	—	12.0 years	17.0 years	—
Duration unknown*	28	24	4	14

*Patients who did not know they had heart disease until coming to clinic or without a history of previous rheumatic manifestations.

TABLE V. EFFECT OF AGE ON HEART FAILURE

AGE GROUPS IN YEARS	TOTAL	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Under 20	20	18	2	10
20-29	78	69	9	12
30-39	29	23	6	20
40 and over	4	3	1	25
Average age	—	24.3	27.8	—

A history of previous failure was likewise found to be significant. Every patient who decompensated during a previous pregnancy did so again during the observed pregnancy. However, 9 per cent of those who had never had failure before developed it during the observed pregnancy (Table VII).

It has been stated that when the aortic valve is damaged the patient faces a greater risk during pregnancy than when the mitral valve alone is involved.^{15,28,39} Our experience does not confirm this observation. Table VIII shows that failure

*The classification of the New York Heart Association was used:⁵

Class I: Patients with cardiac disease and no limitation of physical activity;

Class II (formerly 2a): Patients with cardiac disease and slight limitation of physical activity;

Class III (formerly 2b): Patients with cardiac disease and marked limitation of physical activity;

Class IV: Patients with cardiac disease and who are unable to carry on any physical activity without discomfort.

was more than twice as common in patients with mitral valvular disease alone (24 per cent) than it was in those who had aortic or combined aortic and mitral valvular disease (11 per cent).

TABLE VI. EFFECT OF FUNCTIONAL CAPACITY ON FAILURE

FUNCTIONAL CLASSIFICATION*	TOTAL PATIENTS	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Class I	37	37	0	0
Class II	45	44	1	2
Class III	47	32	15	32
Class IV	2	0	2	100
Total	131	113	18	14

*Classification of the New York Heart Association.

TABLE VII. CORRELATION BETWEEN PREVIOUS HEART FAILURE AND FAILURE IN OBSERVED PREGNANCY

	TOTAL	NUMBER OF PATIENTS WHO DID NOT FAIL IN OBSERVED PREGNANCY	NUMBER OF PATIENTS WHO FAILED IN OBSERVED PREGNANCY	PER CENT PATIENTS WHO FAILED IN OBSERVED PREGNANCY
Patients who had heart failure previously	9	2*	7	79
Patients who had no heart failure in the past	122	111	11	9
Total	131	113	18	14

*These two patients failed during an attack of acute rheumatic carditis and not during pregnancy.

TABLE VIII. EFFECT OF VALVULAR LESIONS ON FAILURE

VALVULAR LESIONS	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PER CENT PATIENTS IN FAILURE
Mitral insufficiency with enlarged heart	30	1	3
Mitral stenosis and mitral insufficiency	58	14	24
Aortic insufficiency alone or with other valvular lesions	27	3	11
Total	113	18	14

The size of the heart was determined by teleroentgenograms at several intervals during and after pregnancy in forty-nine patients who did not fail and in ten who did. The maximum transverse diameter of the heart was measured and the per cent enlargement was calculated according to the table of Ungerleider and Clark.⁴⁰ The weight of the patient at the time the radiogram was taken was used uncorrected when making the calculations. The results thus obtained approximated the post-partum cardiac measurements within a range of 10 per cent or less. Cardiac measurement by such a method therefore seems reliable, even though the configuration and position of the heart changes as gestation advances. None of the patients whose hearts were enlarged less than 10 per cent above normal had failure. Contrariwise, all patients who failed showed an increase of 10 per cent or more above normal. However, a number of women with 20 to 30 per cent enlargement did not experience decompensation. It was concluded from this that while patients with minimal cardiac enlargement are better risks, those with moderate enlargement are not necessarily bad risks. In so far as these limited observations indicated, there was a general but not a strict correlation between the degree of enlargement and the likelihood of failure.

The prognosis in all patients with rheumatic heart disease, men and women, has been found to be more favorable when the original manifestations consisted of chorea or muscle and joint pains rather than polyarthritis or carditis.⁴¹⁻⁴⁴ We have found this to be true also for pregnant cardiac patients. None of the patients who had had chorea or muscle and joint pains as the sole rheumatic manifestation developed failure during the observed pregnancy. Five of the forty-seven patients who had had polyarthritis alone, and six of nine patients who had had both polyarthritis and chorea became decompensated. The average duration from the first rheumatic manifestation to the observed pregnancy in this last group was eighteen years, whereas in the group that had chorea alone it was fourteen and one-half years. This difference may account in part for the greater incidence of failure. Although the groups are not large enough to be

TABLE IX. EFFECT OF PARITY ON HEART FAILURE

AGE GROUP IN YEARS	PRIMIPARA		MULTIPARA	
	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE	PATIENTS NOT IN FAILURE	PATIENTS IN FAILURE
Under 20	12	2	6	0
20-29	28	4	41	5
30-39	2	1	21	5
40 and over	0	0	3	1
Total	42	7	71	11
Per cent patients in failure	—	17	—	15

suitable for statistical analysis, nevertheless, this observation seems to us to merit further study since it may have clinical importance. Evidently polyarthritis, or a combination of polyarthritis and chorea, implies severer infection and, hence, greater cardiac damage than chorea alone.

There seemed to be no significant difference in the rate of failure among primiparous as compared with multiparous women (Table IX).

DISCUSSION

The natural history of rheumatic heart disease may be said to consist of four phases: (1) an initial infection which may be manifested by carditis, polyarthritis, chorea, or muscle and joint pains; (2) one or more recrudescences which, like the primary episode, may follow a hemolytic streptococcic infection; (3) an inactive period, lasting usually from puberty or adolescence to the fourth or fifth decade, in which there are usually no recurrences or evidence of decreasing functional capacity; and (4) a diminution in cardiac reserve leading progressively to congestive heart failure and later death. When auricular fibrillation supervenes, it usually occurs during the last phase and is essentially a reflection of the long duration of the disease.

Phase 1, the initial infection, usually occurs in childhood. It does not always precede heart disease. Twenty per cent or more of adult patients give no history of having had any previous rheumatic manifestations. Phase 2, recurrences of rheumatic fever, rarely complicates pregnancy. Phase 3, the period when the heart disease is inactive, is the one during which pregnancy usually occurs and this explains why the majority of patients do well when under intelligent obstetrical care. Phase 4, diminished cardiac reserve and failure, is seen in less than one-fourth of the pregnancies. It is of utmost importance to recognize when a woman who is pregnant or contemplating pregnancy is approaching this phase. Cardiac failure ranks first among the causes of maternal deaths in patients with heart disease and is the only cause amenable to therapy, especially when detected early. In addition, as has been demonstrated, the chances of having a live baby are dependent to a large degree on the mother not developing heart failure.

How long a given patient is likely to remain in Phase 3 before entering Phase 4 will depend, in the main, on the number of years that have elapsed since the initial infection, the severity and nature of this infection (carditis is more serious than polyarthritis and the latter is more severe than chorea), the frequency and number of recurrences, and the age of the patient. When there is no previous history of any rheumatic manifestation by which to determine the duration of the disease, the absolute age of the patient may be used as a rough index.

Complications such as subacute bacterial endocarditis, embolization, intercurrent infections, and so forth, may occur in any phase and may seriously alter the course of events as here outlined.

Effect of Pregnancy on Duration of Life.—The question of whether pregnancy alters the course of rheumatic heart disease or shortens the life of the patient is

of fundamental importance. In several groups, the reported age of death was younger in nulliparous than in parous women.²⁸ When the sample was reduced to include only those who lived to a "marriageable age," the same results were obtained.^{32,45} When, furthermore, only those who died of congestive heart failure were considered and the group subdivided into those who survived past the age of 18 years and those who survived past the age of 40 years, there was no significant difference in the average age at death between nulliparous and parous women.⁴⁵ In this last group, those who died during pregnancy were not included.

The reports just quoted are subject to some criticism. Several important factors in the nulliparous and parous groups were not controlled; these include age at onset of heart disease, number and severity of recurrences of rheumatic fever, functional capacity of the heart, and the respective duration from onset of heart disease to failure and from failure to death. These factors were carefully considered and controlled in an analysis made by Cohn and Lingg⁴⁶ who compared the clinical course and life span of 169 women, who bore one or more children after they were known to have developed rheumatic heart disease, with the course of 215 nulliparous women who had the same disease. All patients in both groups were observed in the clinics of the New York Heart Association to the time of death. The groups were comparable in that each consisted of a similar proportion of patients who developed heart disease before the childbearing period (age 19) and after, who had mild heart disease with good functional capacity, and who had severe heart disease with impaired cardiac reserve or episodes of congestive failure. The analysis showed that there was no significant difference in the tempo of the clinical course, the rate of development of congestive heart failure, the duration of life from onset of disease to death, and the age at death in the parous and the nulliparous groups.

This reassuring conclusion applies only to those who survive the period of gestation. Pregnancy entails certain risks for the patient with rheumatic heart disease which one who is not pregnant obviously does not face. Failure or death may occur during or soon after pregnancy which may not have resulted had the patient not been pregnant. Assuming, however, that the patient does survive the pregnancy, the subsequent course will very likely remain unaltered.

Age: Patients with rheumatic cardiac disease, regardless of parity, are more prone to fail as they get older. In a group of 644 adult cardiacs (male and female), the average age of failure was 30 years.⁴ It is apparent, then, why many observers^{6,22,28,47} have stressed age as an important guide in the prognosis of pregnant cardiac patients. Patients above the age of 30 years, and especially above 35 years, are much more apt to decompensate than those who are younger.

Duration: If the time of onset of heart disease were known, then the duration from onset to pregnancy would undoubtedly be more dependable as a prognostic guide than the absolute age of the patient. Lacking this precise information in all cases, we have arbitrarily taken the first rheumatic manifestations as the time of onset. This does not imply that the heart disease necessarily begins at this time. As has been mentioned, there is a closer correlation between duration of disease and failure than between absolute age and failure.

Enlarged Heart: That the heart actually increases in weight during pregnancy has not yet been clearly demonstrated. In women with similar rheumatic valvular lesions who died of congestive heart failure, the heart was found to be of approximately the same weight at autopsy regardless of whether the patients had no, few, or many pregnancies.⁴⁵ Thus, it is likely that pregnancy causes no permanent cardiac enlargement. Since the heart increases in size as the duration and severity of the disease increases, the risk of failure is naturally greater in pregnant women whose hearts are markedly enlarged.^{13,48-50} Yet heart size, per se, we have found not to be as significant an index of prognosis as other factors here considered.

Valvular Lesions: There is no unanimity of opinion as to the seriousness of the combination of mitral stenosis and aortic insufficiency as compared with mitral stenosis alone. Some observers attach grave significance to the coexistence of mitral and aortic lesions,^{15,28,30} and others state that there is no significant difference between the two groups.^{49,51} This divergence of opinion also exists among students of rheumatic heart disease in general.⁵² Our experience corresponds with those who attribute no greater gravity to combined aortic and mitral valvulitis than to mitral stenosis alone. This is substantiated by the fact that data collected by us from reports published since 1936 show no important difference between the mortality rates among pregnant women with combined mitral and aortic valvulitis and those with mitral valvulitis alone (Table X)

Functional Class and Previous Failure: The functional capacity of the heart to do work is without doubt the most reliable single index of the prognosis in pregnancy. At times, however, it is difficult to establish this with precision and, again, it may vary from one month of pregnancy to another. An actual test of pregnancy is, therefore, more reliable; hence it is evident that a patient who has failed in a previous pregnancy will almost certainly decompensate again unless failure was due to circumstances not likely to recur, such as active rheumatic carditis.^{22,54-57} The contrary is not true, that patients who have not failed previously will not fail in a later pregnancy. In our series, 11 per cent of the multiparous patients who had no history of failure decompensated during the observed pregnancy.

Multiparity: Conflicting opinions have been expressed on parity: such as, the prognosis is worse in primiparas;⁵⁰ it is worse in multiparas;^{15,58} parity, per se, has no important bearing on the prognosis.^{47,56} This discrepancy may have resulted from the fact that the different authors did not control to the same degree, at least, two factors that influence the outcome, namely, the duration of heart disease (longer in multiparas) and the physical effort spent in obstetrical labor (greater in primiparas). When allowance is made for both factors, it seems reasonable to conclude that parity, per se, is of no real significance.

There are a number of factors that should be considered in evaluating the prognosis of pregnancy in patients with heart disease. Some of these are more important than others, but each of them fits into a more inclusive principle which is based on the orientation of the patient in the natural course of her heart

disease. The validity of applying this principle to pregnant cardiac patients is supported by the evidence that gestation does not alter the course of the disease.

TABLE X. DEATHS AMONG PREGNANT RHEUMATIC CARDIAC PATIENTS GROUPED ACCORDING TO VALVULAR LESIONS (1936 TO 1946)

	NUMBER OF PATIENTS WITH MITRAL VALVULITIS ALONE	NUMBER OF DEATHS	PER CENT DEATHS	NUMBER OF PATIENTS WITH AORTIC OR AORTIC AND MITRAL VALVULITIS COMBINED*	NUMBER OF DEATHS	PER CENT DEATHS
Hay (1939) ⁹	56	1	1.8	10	0	0
Harris (1937) ¹²	81	6	7.4	19	2	9.5
Lamb (1937) ¹³	89	5	5.6	12	2	16.7
Naish (1937) ¹⁵	349	10	2.9	78	2	3.9
Bramwell and Longson (1939) ²³	260	20	7.7	31	1	3.2
Jensen et al. (1940) ²¹	88	6	6.8	11	1	9.1
Hamilton and Thompson (1941) ⁶	581	28	4.7	148	8	5.3
Stromme and Kuder (1946) ⁵³	565	7	1.2	90	1	1.1
Total	2,069	83	4.01	399	17	4.26

*Forty-seven of these 399 patients had aortic valvulitis alone, 352 had combined mitral and aortic valvulitis.

SUMMARY

In determining the prognosis in pregnancy of 142 women with rheumatic heart disease, the following factors were considered: duration of rheumatic fever, age, functional capacity, history of previous failure, type of valvular damage, size of heart, nature of earlier rheumatic manifestations, and parity. It was found that the important signs were those which helped prognosticate congestive failure. That failure is the governing feature in prognosis is supported by the observations (1) that it is the most common cause of death in pregnancy complicated by rheumatic heart disease and (2) that the infant mortality rate for our group of patients with congestive heart failure was three times as high as for patients who had heart disease without failure and four times as high as for normal pregnant women delivered on the same obstetrical service.

The factors found to be important in prognosticating failure and in estimating the risk involved in pregnancy form integral parts of a basic principle, which consists of establishing the patient's position in the natural course of her rheumatic

heart disease. This principle gains validity when data collected under well-controlled conditions indicate that pregnancy per se does not alter the course of this disease. The application of this principle for determining prognosis led to interruption (per vagina) of only eleven of 142 pregnancies. No hysterotomies were performed after the patient was permitted to pass through the first trimester of pregnancy. There were no deaths from congestive heart failure among the 129 patients who remained under our care through pregnancy and parturition.

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NEWER CONCEPT OF STOKES-ADAMS SYNDROME

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STOKES-ADAMS attacks are generally believed to be due to periods of ventricular asystole occurring in patients with heart block. The Criteria Committee of the New York Heart Association defined this syndrome as "attacks characterized by unconsciousness, often accompanied by muscular twitchings and even generalized convulsions. These attacks occur in patients with auriculo-ventricular block when the ventricular diastole is sufficiently prolonged to result in a severe grade of cerebral ischemia. The duration and severity of an attack depend on the length of ventricular diastole. This term is not applied to syncope due to other causes."¹

White^{2, p. 677} described the syndrome as "the association of syncope and convulsions with marked slowing of the heart's action. . . All grades of disturbances of the cerebral circulation may exist from slight dizziness and faintness with transient ventricular standstill of two or three seconds, duration up to extreme degrees of the Adams-Stokes syndrome with cessation of the heart beat for as long as twenty or thirty seconds."

These definitions reflect the widely-held belief that ventricular standstill is the only disturbance of the cardiac mechanism which, supervening in heart block, causes loss of consciousness. However, for many years individual case reports recurring in the medical literature indicated the probability that other cardiac arrhythmias might be responsible for the attack in patients with heart block.*

Finally, Parkinson and associates,³ in 1941, reviewed all reported cases of Stokes-Adams syndrome in which electrocardiographic tracings were obtained during the attack. Their findings indicate that only 55 per cent of attacks were associated with ventricular asystole. The remainder were due to various combinations of ventricular tachycardia, ventricular fibrillation, and ventricular asystole.

On the basis of this study, Parkinson defined Stokes-Adams disease as the "name applicable to patients with heart block who suffer from recurrent attacks of loss of consciousness due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or a combination of these."³

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*The authors of these reports will not be cited in this communication since they have been included in a paper by Parkinson and associates.³

The following case is reported because it graphically records in a single patient the different arrhythmias which may precipitate a Stokes-Adams attack. It is also presented as additional evidence against the erroneous concept that ventricular asystole is the sole mechanism precipitating these attacks.

CASE REPORT

A colored woman, 70 years of age, was admitted to the hospital because of repeated convulsions during the preceding twenty-four hours. One week previously, she had noted increasing shortness of breath and inability to carry on her usual activities. Otherwise, her history was negative for hypertension, syphilis, anginal attacks, decompensation, or syncopal episodes. She had had approximately fifteen attacks of convulsions before entering the hospital. The onset

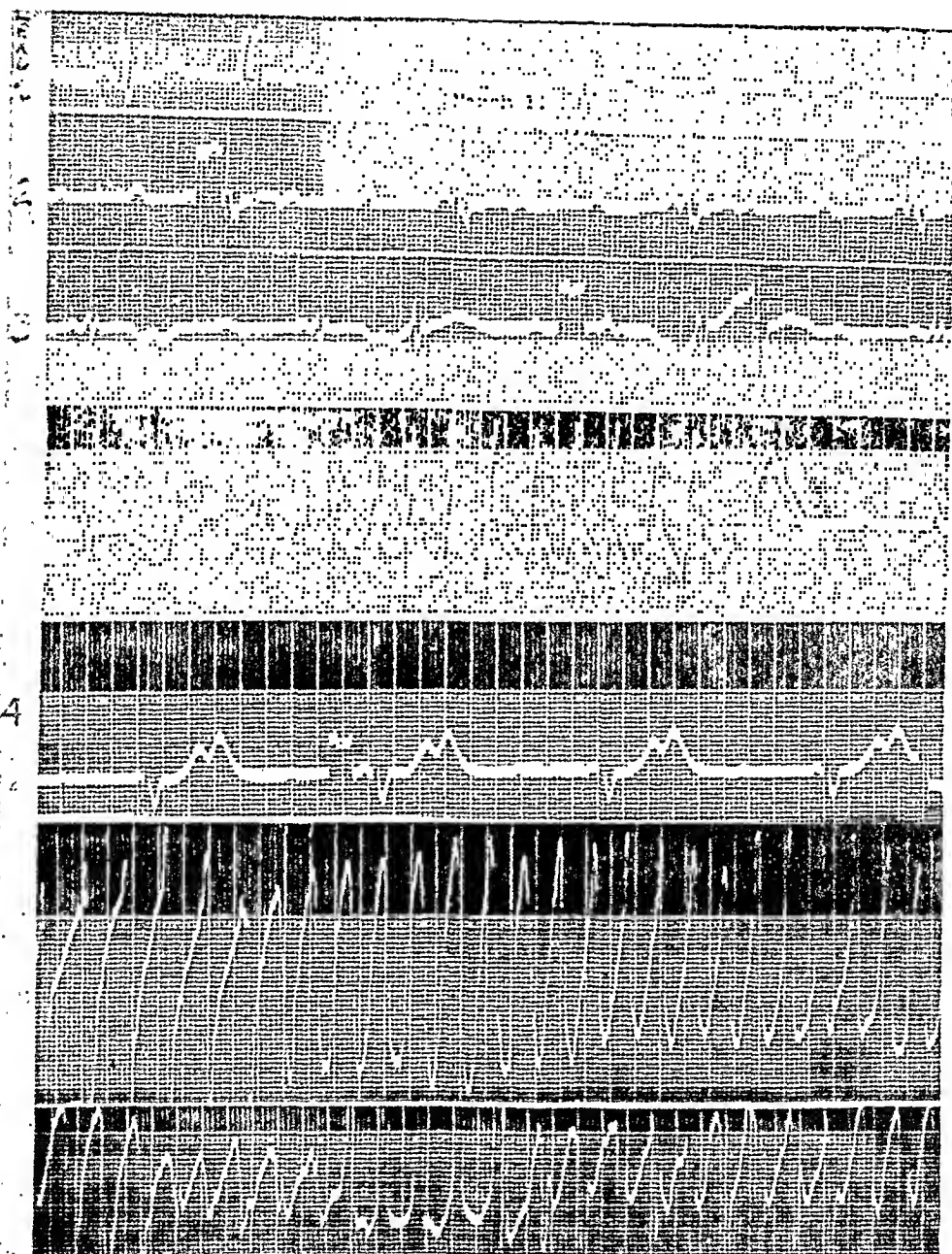


Fig. 1.—Electrocardiogram on admission showing complete auriculoventricular dissociation, with runs of ventricular tachycardia.

of the attack was usually preceded by periods of rapid heart action, which increased in frequency and duration until unconsciousness occurred.

Physical examination in the intervals between convulsions revealed the patient to be in no apparent distress. She was entirely comfortable lying flat in bed. Her heart was not enlarged. The ventricular rate was regular at a rate of 20 beats per minute with an occasional extrasystole. In the intervals between the ventricular beats, fainter beats were audible at 72 per minute, and these were synchronous with the venous pulsation in the neck. The heart sounds were of good quality and no murmurs were present. The arterial pressure was 200/90. There was no evidence of decompensation. Gross neurological examination revealed no abnormality.

The diagnosis was complete A-V heart block with Stokes-Adams syndrome. She was given ephedrine sulfate orally, three-eighths of a grain, every three hours. The following morning an electrocardiogram confirmed the presence of complete auriculoventricular dissociation, but also indicated runs of ventricular tachycardia (Fig. 1). The possibility that ephedrine might be responsible for the ectopic rhythm, and might further precipitate ventricular fibrillation, caused us to discontinue the drug and prescribe quinidine sulfate in doses of 15 grains four times daily. During the next few days, electrocardiographic tracings were obtained during many Stokes-Adams attacks. The patient was asymptomatic during the periods of complete heart block, but cerebral manifestations were likely to occur when other cardiac arrhythmias supervened. These arrhythmias, recorded during several different attacks, included the following: ventricular fibrillation followed by ventricular tachycardia (Fig. 3); ventricular tachycardia followed by ventricular asystole (Fig. 3); ventricular asystole alone (Fig. 2); ventricular tachycardia followed

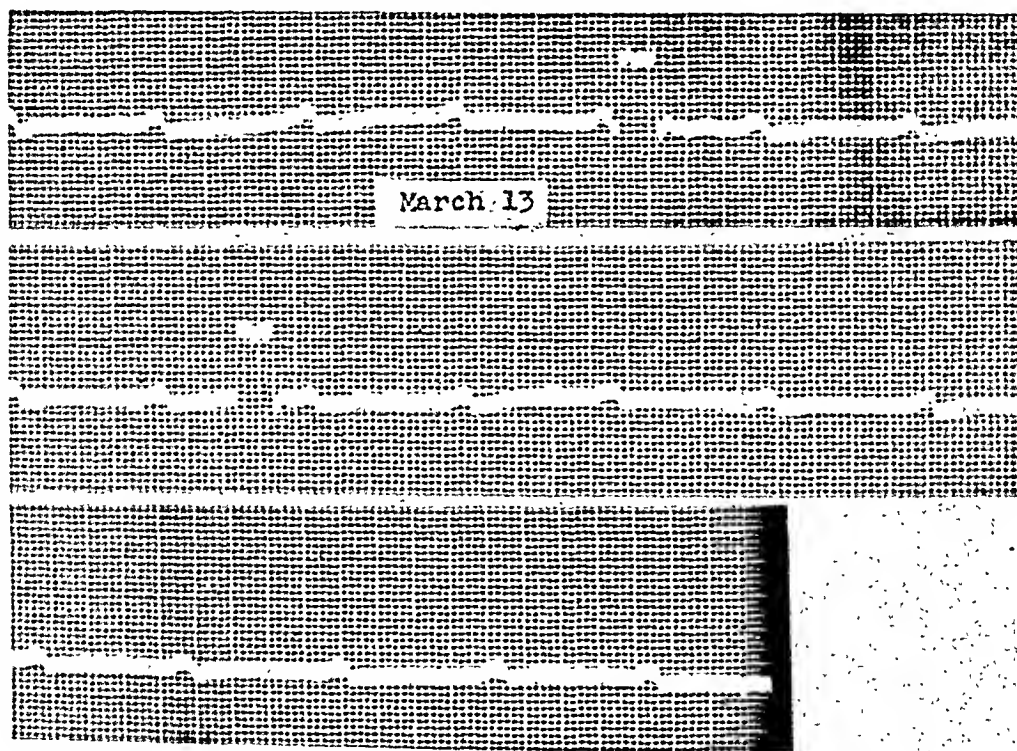
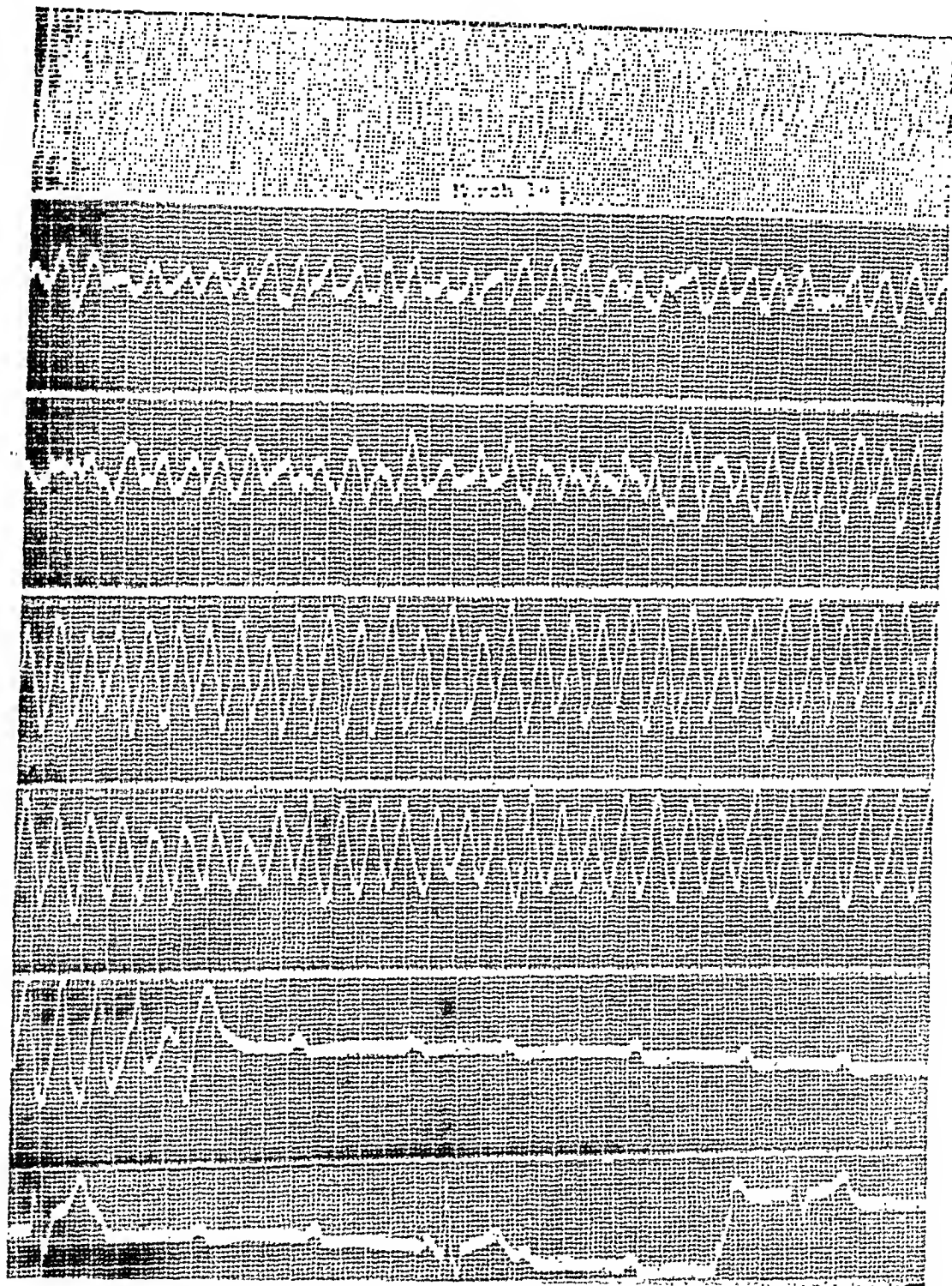


Fig. 2.—Continuous tracing of Lead II showing ventricular asystole of fifteen seconds during a Stokes-Adams attack.

by ventricular fibrillation, ventricular tachycardia, and ventricular asystole (Fig. 3); and finally, ventricular tachycardia followed by ventricular fibrillation and ventricular asystole (Fig. 4).

During the first three days, it was apparent that the patient was becoming worse in spite of a total intake of 132 grains of quinidine, and that this drug could not prevent ventricular tachycardia and fibrillation in her case. It was then decided to treat the block rather than the ectopic

rhythms (Table I). Realizing full well the theoretical contraindication, 1.0 c.c. of a 1:1000 solution of epinephrine was administered into a vein slowly. The patient had no Stokes-Adams attacks during the next hour. Therefore, another 1.5 cc. of epinephrine were given intravenously with no unusual effects. The absence of Stokes-Adams attacks led us to continue epinephrine and ephedrine therapy. During the next five days, the patient was free of attacks, and her improvement was so striking that preliminary arrangements were made to discharge her from the



hospital. On the morning of the sixth day of epinephrine therapy, the patient developed a right hemiplegia and a temperature of 102° Fahrenheit. Later that day, râles appeared in the bases of the lungs, the patient became comatose, the temperature rose to 104.5° F., and she succumbed the following morning. The electrocardiogram obtained the afternoon before exitus (Fig. 5) revealed no significant changes from the original electrocardiogram. The progressive increase in rate of the auricular and ventricular complexes following epinephrine therapy is evident in Fig. 6.

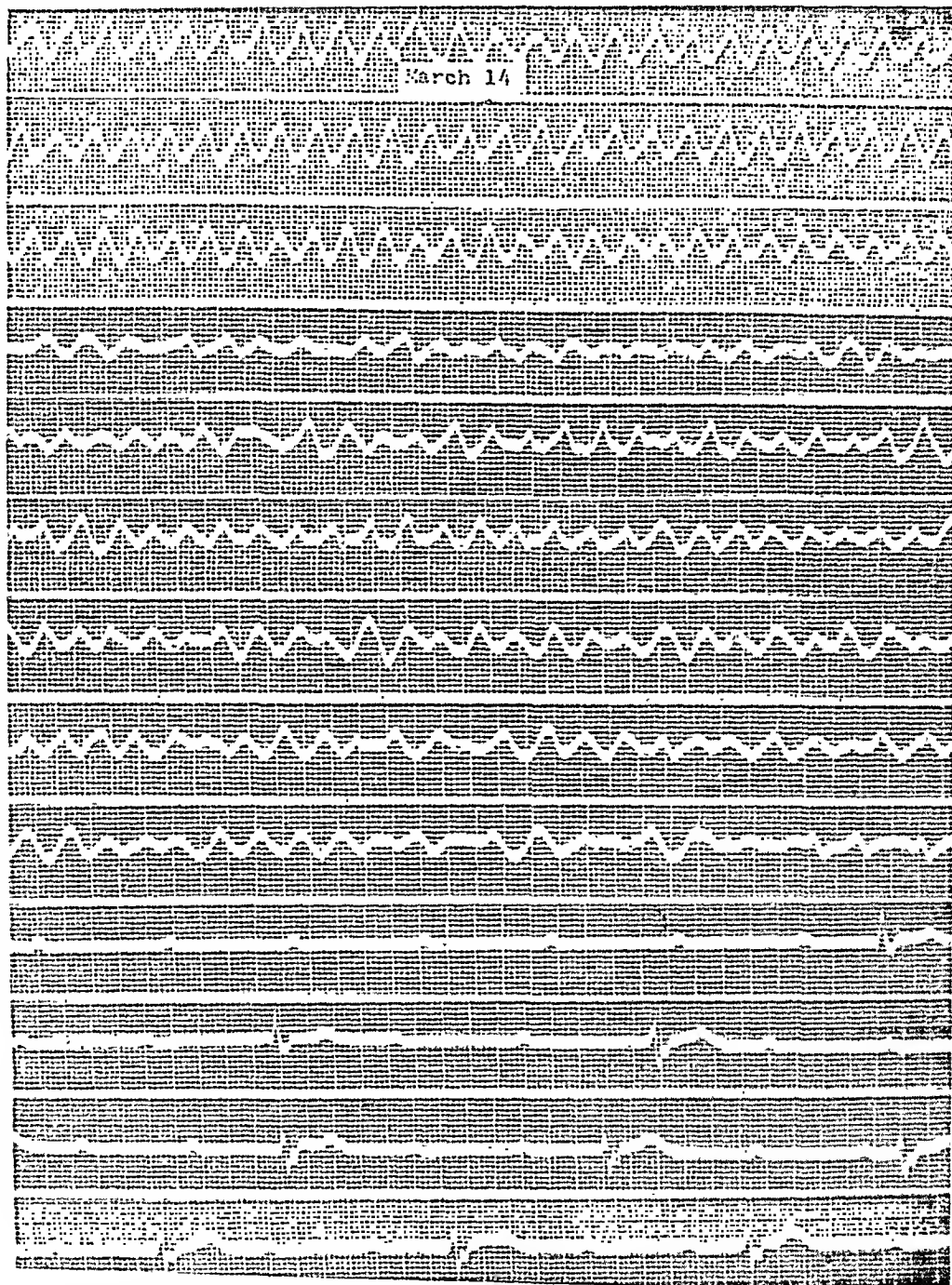


Fig. 4.—Continuous tracing of Lead II during Stokes-Adams attack showing ventricular tachycardia, ventricular fibrillation (forty-one seconds), ventricular asystole, and return to basic rhythm (complete heart block).

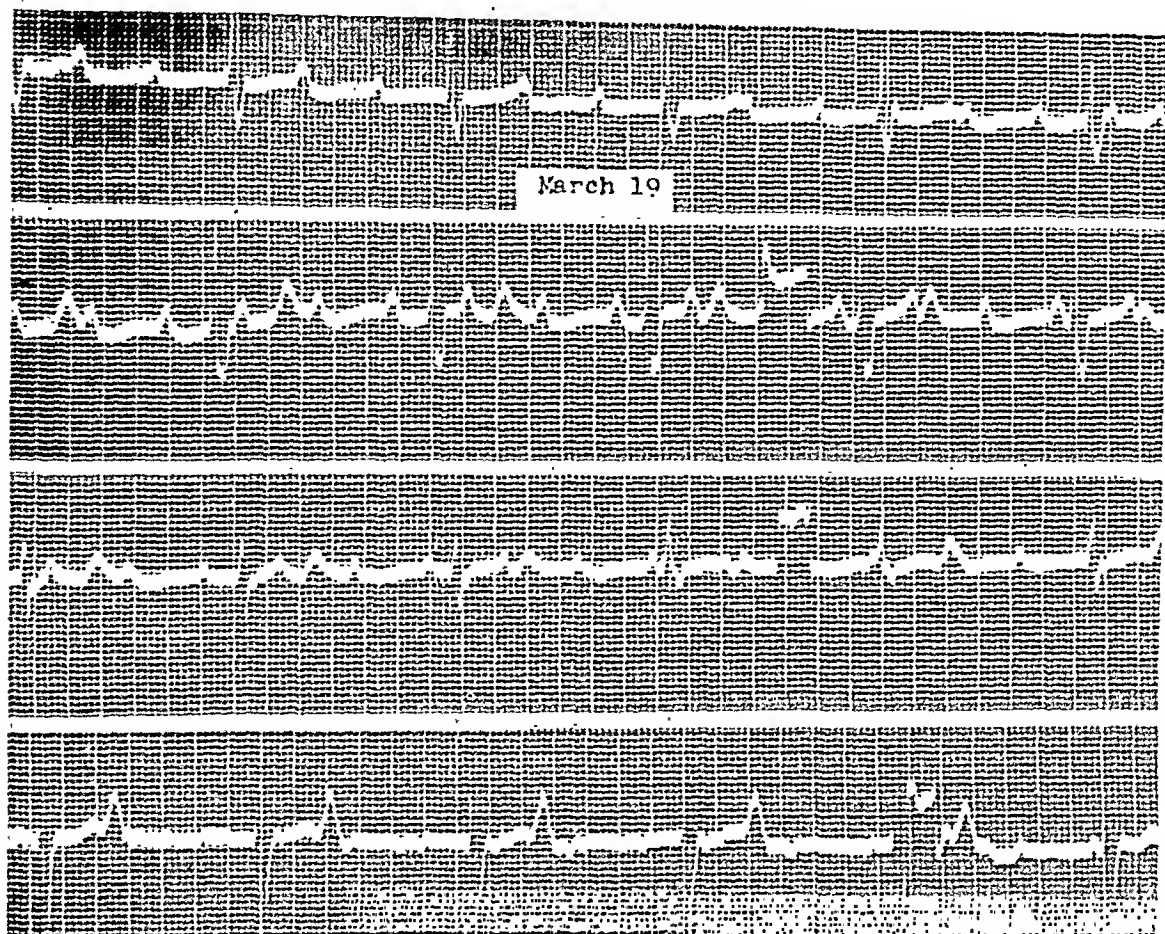


Fig. 5.—Electrocardiogram the day before exitus showing complete auriculoventricular dissociation, with an auricular rate of 120 and ventricular rate of fifty per minute. The contours show no significant difference from those taken on admission.

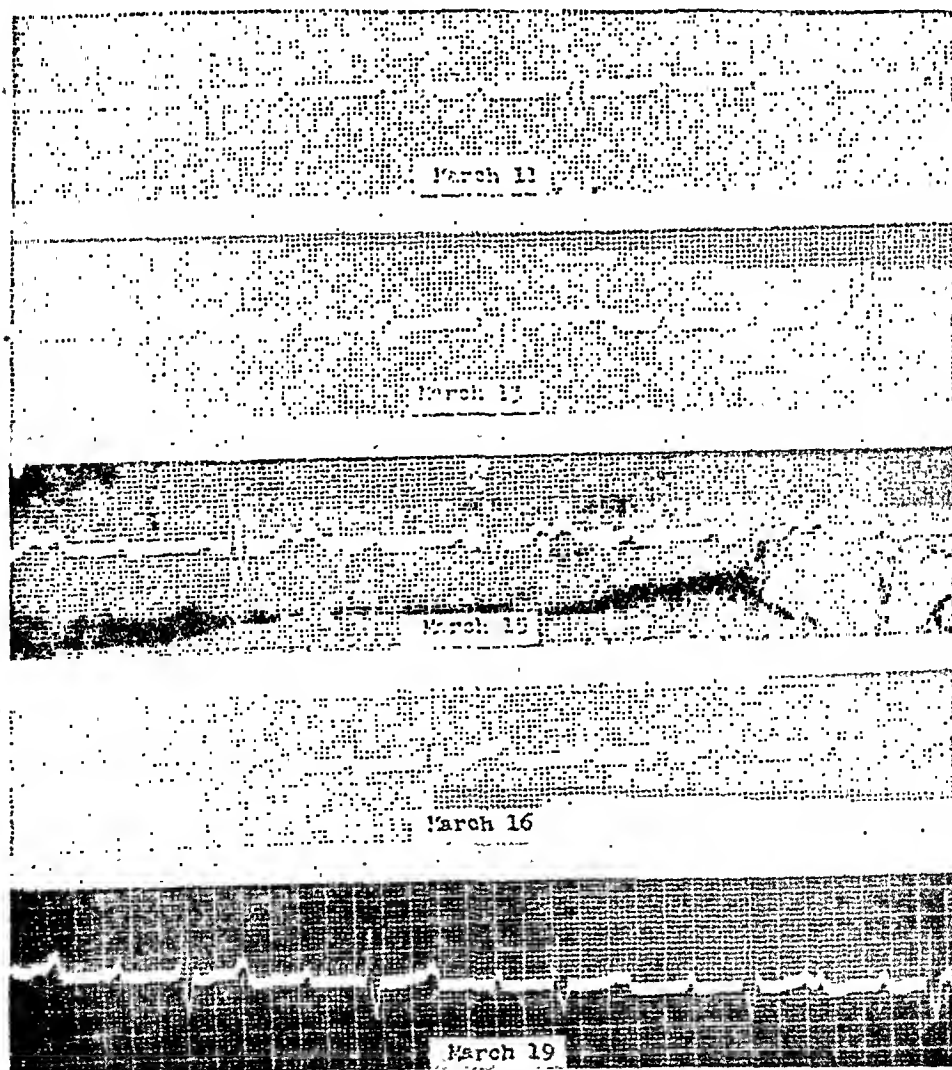


Fig. 6.—Lead II showing progressive increase of auricular and ventricular rates due to epinephrine therapy.

The significant findings at post-mortem examination* were in the brain and heart. The brain revealed slight to moderate generalized edema without evidence of hemorrhage, discoloration, or softening. A moderate amount of atherosclerosis was noted in the arteries, most evident in the basilar vessels. Thrombi were not demonstrable, and no obvious cause for the hemiplegia could be established.

TABLE I. SUMMARY OF CLINICAL COURSE

DATE	CONVULSIONS	DIAGNOSIS	TREATMENT
3-10	Present	* CHB, VA, CHB	Ephedrine gr. 3/8 q 4 hr. (2 doses)
3-11	Present	** CHB, VT, CHB (Fig. 1)	Quinidine gr. 15 Q.I.D.
3-12	Present	*** CHB, VF, VT, CHB	Quinidine gr. 6 q 2 hr.
3-13	Present	*** CHB, VT, VA, CHB *** CHB, VA, CHB (Fig. 2)	Quinidine gr. 6 Q.I.D. Total quinidine, gr. 132
3-14	Present	*** CHB, VT, VF, VT, VA, CHB (Fig. 3) *** CHB, VT, VF, VA, CHB (Fig. 4) *** CHB, VT, VF, CHB *** CHB, VF, VT, VF, VA, CHB	1 c.c. epinephrine 1:1000 I.V. 1.5 c.c. epinephrine 1:1000 I.V. 1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 6 hr.
3-15	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-16	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-17	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-18	Absent	** CHB	1 c.c. epinephrine oil q 4 hr. Ephedrine gr. 3/8 q 4 hr.
3-19	Absent	** CHB * Right hemiplegia Temp. 102°	Ephedrine gr. 3/8 q 4 hr.
3-20	Absent	** CHB * Right hemiplegia "Hypostatic pneumonia" Temp. 104.6°—Expired	

* Clinical diagnosis

** Electrocardiograph diagnosis

*** Electrocardiograph diagnosis of
Stokes-Adams attack

CHB—Complete heart block

VT —Ventricular tachycardia

VF —Ventricular fibrillation

VA —Ventricular asystole

The heart size was within normal limits. Both coronary ostia were markedly narrowed by atherosclerotic plaques. Approximately 3.5 cm. from the origin of the left coronary artery, the lumen of the anterior descending branch was narrowed to one-fourth its size by a sclerotic plaque 2.0 cm. long. The right coronary artery also contained a sclerotic plaque 4.0 cm. from the ostia which encroached upon the lumen. Gross examination revealed no thrombi, areas of infarction, or fibrosis. Sections through the auriculoventricular node and bundle of His revealed an area of fibrosis and hyalinization which appeared somewhat atypical (Fig. 7). Sections were cut, there-

*Post-mortem examination was performed by Doctors S. A. Wallace and P. Marcuse.



Fig. 7.—Section through A-V node and upper bundle of His showing fibrosis and hyalinization.

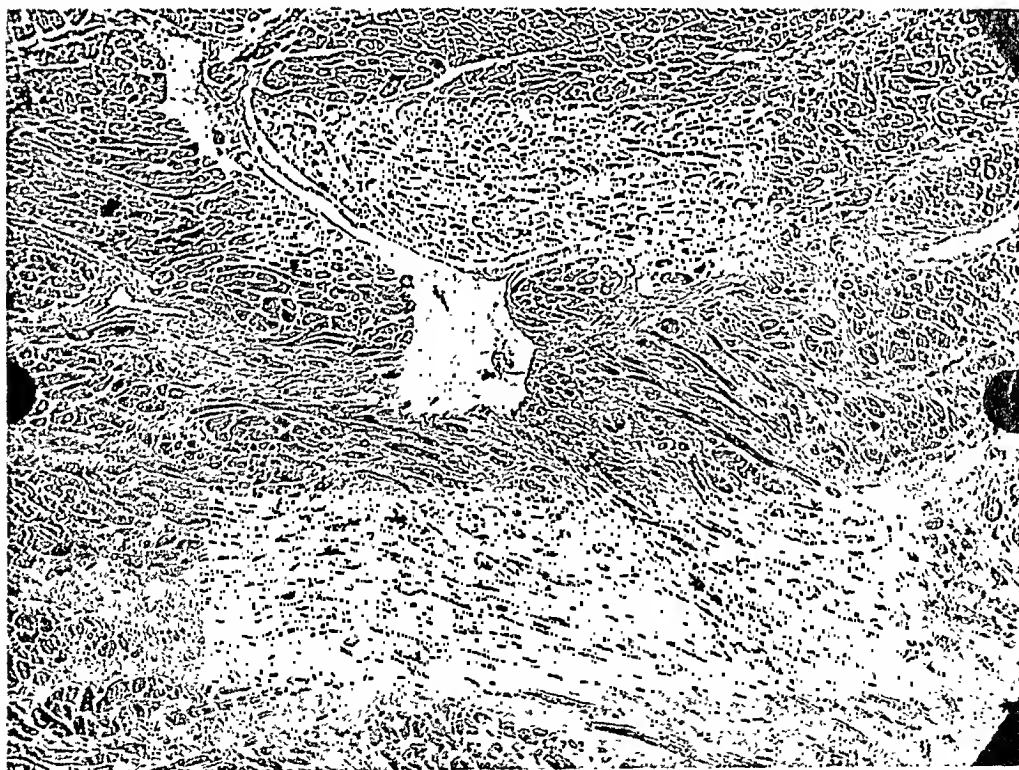


Fig. 8.—Section through A-V node and upper bundle of His in a "normal" heart showing fibrosis and hyalinization similar to Fig. 7.

fore, from normal hearts in the same area, that is, in the junctional tissue just above the interventricular septum behind the posterior aortic valve. These normal hearts revealed a similar type of histologic structure (Fig. 8). Closer study of the gross specimens of the normal and pathologic hearts indicated that our sections included a portion of the fibrous trigone. It was most surprising to us to learn from a review of histology texts that the auriculoventricular node and upper bundle of His are situated in the fibrous trigone.⁴ One wonders how many cases reported in the literature as showing fibrosis of the node or bundle of His have actually had a normal histologic structure. Microscopic sections of the lower bundle, and auricular, septal, and ventricular myocardium revealed nothing of significance.

DISCUSSION

Cardiac Mechanism in Stokes-Adams Attacks.—The cerebral anemia precipitating recurrent syncope and convulsions in this case were due not only to ventricular asystole, which is widely believed to be the sole mechanism, but also to rapid ventricular tachycardia, ventricular fibrillation, and to different combinations of these arrhythmias. It is emphasized that this patient's abnormal cardiac mechanism, graphically demonstrated by electrocardiographic tracings during syncope and convulsions, is not unusual, but has occurred in half of the reported cases of Stokes-Adams syndrome in which electrocardiographic tracings were made during the attack.

It is interesting that in the first description of this disease, Morgagni,⁵ in 1769, quoted his patient as describing "sudden commotions" and "tumultuary motions" of the precordium immediately prior to the attacks. Stokes' patient also noted a "fluttering sensation about the heart" before his attacks.⁶ These sensations are more likely to be due to ventricular extrasystoles and tachycardia than to ventricular standstill, and closely resemble the premonitory symptoms of this case.

Parkinson's definition, which is compatible with the facts and with the historic descriptions of the original cases, is definitely to be preferred to the incomplete, inaccurate definitions in many current textbooks.

Pathologic Anatomy and Physiology of Stokes-Adams Attacks.—It is believed that the auriculoventricular bundle is more sensitive to anoxemia than the undifferentiated myocardium because of its more specialized nature, and its nerve-like function. A partially inadequate vascular supply may cause total functional impairment without causing demonstrable histologic change. Thus, the bundle of His is especially vulnerable in the atherosclerotic age group, in which 80 to 90 per cent of all complete A-V heart block occurs.⁷ The marked coronary sclerosis and partial ostial occlusion impeded the coronary flow to a degree sufficient to explain the heart block in this patient.

One possible explanation for the various arrhythmias observed in this case can be given. In other portions of the myocardium (possibly adjacent to the bundle, and supplied by the same artery), there probably existed a relative, or at least potential, myocardial ischemia due to the same coronary sclerosis, plus the additional hazard of an excessively prolonged diastolic period associated with the heart block. Minor physiologic factors adversely affecting relative coronary blood flow, such as slight lowering of aortic pulse pressure, increased

exercise, increased diastolic time, and so forth, factors which cause no appreciable clinical effect in normal individuals because of adequate reserve, grossly exaggerated the coronary insufficiency and precipitated an irritative myocardial anoxemia. This state was reflected in the ventricular extrasystoles, which still further compromised the coronary flow, progressed to ventricular tachycardia, and finally to ventricular fibrillation. The period of ventricular asystole which followed the rapid ectopic rhythm was evidence of myocardial exhaustion. Recovery from this phase was signaled by an idioventricular beat and return to the basic rhythm. This was the sequence in 70 per cent of the recorded attacks.

Therapy.—The ineffective response to quinidine in this case is consistent with the impression of some clinicians that this drug not infrequently fails to stop or prevent ventricular tachycardia. The present tendency to administer larger and larger doses is an indication that therapeutic failure is not an uncommon occurrence. Whether or not increased dosage will result in greater success awaits further reports. In this case, however, 132 grains of quinidine administered over a period of three days did not prevent ventricular tachycardia and fibrillation. This case poses the question as to whether or not quinidine is the drug of choice in recurrent ventricular tachycardia associated with A-V heart block. Incidentally, a progressively widening QRS complex, which some believe to be a contraindication to further quinidine therapy, was not evident in the tracings.

Epinephrine is known to be a dangerous drug in patients with ventricular extrasystoles and ventricular tachycardia because of the possibility of its initiating ventricular fibrillation. This danger is especially great during cyclopropane and chloroform anesthesia. White^{2, p. 683} warns against its use in ventricular asystole when it is preceded by ventricular fibrillation.

However, in this patient, who apparently had the prime contraindications of recurrent ventricular tachycardia and fibrillation and periods of asystole preceded by fibrillation, epinephrine effectively prevented Stokes-Adams attacks and the arrhythmias which precipitated them. One may surmise that the advantageous effect of epinephrine upon the coronary flow (the increased heart rate and decreased diastolic period, increased aortic pulse pressure, increased contractility, and coronary vasodilation) more than compensated for its potential harmful direct effect upon myocardial irritability.

Cause of Death.—Stokes-Adams syndrome predisposes to three modes of cardiac death. Sixty per cent of these patients die suddenly in a Stokes-Adams attack; the others, of coronary thrombosis or congestive heart failure.⁷

This hypertensive, arteriosclerotic patient succumbed to a typical cerebral episode, although no gross lesion could be demonstrated in the brain, post mortem. There was no evidence that epinephrine had caused a rupture of a cerebral vessel. The final course did not suggest any of the three forms of cardiac death. She apparently had been completely relieved of Stokes-Adams attacks for seven days prior to death.

SUMMARY

1. A case of Stokes-Adams syndrome has been presented which demonstrates graphically that the Stokes-Adams attack was due at different times to ventricular tachycardia, ventricular fibrillation, and ventricular asystole, either alone or in various combinations.

2. Interesting aspects of the physiology, pathology, and therapy in this case have been discussed.

Acknowledgement is made to Dr. Tom Brewer and Mrs. D. Semonds for their assistance in obtaining the electrocardiograms in this case.

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AN ANALYSIS OF CAUSES OF RIGHT AXIS DEVIATION BASED PARTLY ON ENDOCARDIAL POTENTIALS OF THE HYPERTROPHIED RIGHT VENTRICLE

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THE *electrophysiologic causes of right axis deviation* are clear cut. In the frontal plane of the body, delineated by Einthoven's triangle, deviation of the mean manifest potential to the right of a line drawn through the center of this plane, perpendicular to the horizontal side of the triangle, can only result when, during excitation of the ventricular muscle, the average potential of the left arm is at a lower level than the average potential of the right arm. Conceivably, this can occur in three ways when reference is made to a predetermined baseline of potential: the right arm may become more positive than the left; the left arm may become more negative than the right; or both processes may occur simultaneously in variable degree.

The anatomic causes of right axis deviation are not quite so definite, and may be multiple in any given instance. Some of the causes usually given are:

(1) Architecture of the Purkinje system: Individual differences in the arrangement of the ventricular conducting system have been used as an explanation of an abnormal axis, largely on the basis of the experiments of Rothberger and Winterberg¹ in dogs. When one considers the complicated embryonic development of the heart and its nervous system, the occurrence of anomalous or aplastic pathways, and hence, of abnormal electrical axes, is not hard to imagine, though not proven.

(2) Preponderance: Lewis² used the term preponderance to indicate that one or the other ventricle was hypertrophied. Although there was agreement in his experiments between the relative weights* of the two ventricles and the electrocardiographic findings, he was careful to point out³ that in some instances of mitral stenosis, "preponderance, as estimated by weighing, is not discovered

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*The right ventricle and the left ventricle were separated from the septum, and the three resulting pieces weighed. A review of Lewis' paper² will show that his method was such as to include with each chamber, elements of muscle undoubtedly activated in a direction away from the cavity toward the septum. Such septal elements have an "electrical weight" opposed to that of the free walls.

in the expected ventricle. Neither are electrocardiographic signs of right hypertrophy discovered in all instances of mitral stenosis." Herrmann and Wilson⁴ corroborated these findings in general, and presented evidence that the form of the ventricular complex and the relative weights of the two ventricles were closely inter-related only when there was considerable hypertrophy of the heart.

For the sake of completeness, the term preponderance may be expanded to include another situation. It is conceivable that sufficient muscle may undergo necrosis in the left ventricle and in the septum to cause preponderance of the right ventricle and right deviation of the electrical axis.⁵ In a sense, this would result in a relative hypertrophy of the right side as a result of "atrophy" of the left side; the heart's center of gravity would be shifted to the right.

(3) Position of the heart: That the lie of the heart in the chest is important in determining the electrical axis was recognized long ago by Einthoven and associates,⁶ Pardee,⁷ Cohn,⁸ Lewis,³ and by Herrmann and Wilson.⁴ More recently, it has become quite clear from a study of extremity potentials* that when the heart lies vertically in the chest the potential of the left arm may be negative, presumably because the origin of this extremity is then opposite the basal orifices of the heart.⁹ If, as sometimes happens, the left arm is more negative on the average than the right, the standard leads will display an angle alpha in excess of $+90^\circ$. Einthoven and associates⁶ knew that the position responsible for such an electrocardiogram was the result of clockwise rotation of the heart not only about an anteroposterior axis, but also about a vertical axis.

The importance of position of the heart in the thorax, even when enlarged, in relation to the electrocardiographic findings was emphasized by Cohn.⁸ Recent observations bear out his thesis. With regard to precordial leads, it is well known that a late RS or intrinsicoid¹⁴ deflection, usually ascribed to a thickened underlying ventricular wall, is encountered in leads from the right side of the precordium in less than one-third of the patients with right ventricular hypertrophy secondary to mitral stenosis.^{†15} Possibly a higher percentage, but by

*In recent years, the term "unipolar leads" has been applied to these records, and clinicians have come to use the term "unipolar" only in relation to these leads. Actually, the term "unipolar" in electrocardiography was first used by Groedel.¹⁰ In its broader sense, it means that a lead has been made in such a way that the potential variations of the exploring (near) electrode are very much greater than the potential variations of the indifferent (distant) electrode. More specifically, it has come to mean a lead in which the zero-potential electrode of Wilson and associates has been used.¹¹ In a sense it is a misnomer, for no lead can be strictly unipolar even when the indifferent electrode is known to be at zero potential. But aside from this, a unipolar lead, as long as one electrode is nearer the source of potential than the other, may be obtained from any point on the body. Thus, we may speak of unipolar extremity leads (V_R , V_L , and V_F), unipolar precordial leads, unipolar esophageal leads, and unipolar intracardiac leads. For the last fourteen years all unipolar records have been made in this laboratory with the electrode of Wilson, Macleod, and Barker.¹¹ Augmentation¹² is occasionally used when recording extremity potentials, but the electrode described by Goldberger¹² is not used because, at times, records made with it display considerable variation from records similarly made with the electrode of Wilson and associates.¹⁴

†It has heretofore been believed¹⁶ that the beginning of the intrinsic deflection or peak of R wave in direct leads marks the time of arrival of excitation under the exploring electrode. The experiments of Cole and Curtis^{17,18} would seem to indicate that the end, rather than the beginning, of this deflection represents the occurrence of complete activity in underlying muscle. In semidirect (precordial) leads, the problem is complicated in proportion to the size of the variables defined by Poisson's integral,¹⁹ and an intrinsic deflection as such is sometimes difficult to recognize. This more often is true of its termination than of its origin. For this reason, the term "intrinsicoid" is applied to the RS deflection in precordial

no means all of such deflections are late, particularly in Lead V_1 , in congenital heart disease with right ventricular hypertrophy and in advanced chronic cor pulmonale. Another interesting feature of these records is that the R wave, when late, is usually later than a similar, smaller deflection recorded from the left side of the precordium, and is sometimes preceded by a Q wave. Assuming that thickness of the wall determines lateness of the intrinsicoid deflection, the clinical observations are not in accord with the pathologic, for in acquired heart disease a free right ventricular wall thicker than the left is almost never seen. Even in congenital heart disease it is not usual, except in the rare defect of uncomplicated pulmonary or infundibular stenosis.* Further, if the deflection were the result of right ventricular hypertrophy one would expect to see, more often, intermediate values which depend upon the extent of the hypertrophy. The occurrence of a small R wave and a deep S wave, and an absence of Q wave, in leads from the left side of the thorax in some of these cases is unexplained.

These data raise several questions: Is the late arrival of excitation on the right side of the thorax in the patients under consideration really caused by right ventricular hypertrophy, or does position of the heart in some way determine it? As a corollary, not particularly related to position of the heart, one might ask whether hypertrophy alone, in the case of the right ventricle, gives rise to a late large R or R' in semidirect leads which are beyond a reasonable doubt in the electrical field of this chamber, or are other factors, such as partial defects in conduction on the right, responsible for it? To be answered also are the influence of left ventricular excitation on electrical events recorded over the right ventricle, and of the size as opposed to the thickness and weight of the right ventricle, in determining the occurrence of the deflection in question.

(4) Intraventricular block with normal QRS interval: There are electrocardiograms which display a late intrinsicoid deflection in one or several leads from the right side of the precordium with a QRS interval of less than 0.1 second.²⁰ These electrocardiograms may or may not display right axis deviation in the standard leads, and the patient may or may not show clinical or other evidence of cardiac disease. It is suspected that the curves obtained probably result from a partial defect in conduction on the right side. Further reference to this anatomic cause of right axis deviation will be made in a discussion of the last case to be presented.

SIMILARITY OF STANDARD LEADS WHEN RIGHT AXIS DEVIATION IS CAUSED BY DISSIMILAR ANATOMIC DEFECTS

In Fig. 1 are shown three standard electrocardiograms with characteristics in common. They differ principally in voltage and by the presence of a small

leads as first used by Macleod, Wilson, and Barker¹⁴ who, in introducing this term, undoubtedly had in mind the differences in this deflection as compared to the analogous one in direct leads.

Because of the practical difficulties involved in measuring the end of the intrinsicoid deflection, we have continued to use the beginning as a standard reference point. Whenever possible, a measurement of the size and duration of the potential developed across the subjacent wall has been made from the peak of Q or beginning of R when Q is absent, to the peak of S or the end of R when S is absent.

As will be seen it is particularly difficult to tell when the endocardium of the subjacent right ventricle has been excited.

*Of twenty cases found in the literature, sixteen showed a right ventricle thicker than the left.

R wave in Lead I of Patient C. Other features, such as a large QS or S in Lead I, and notched or slurred R waves and absence of S waves in Leads II and III, are similar. Also comparable are the T waves which have a direction opposite to the principal QRS deflections. All three patients were taking digitalis. The anatomic findings in each case were as follows:

Patient

- A Mitral stenosis, mitral insufficiency, and questionable aortic insufficiency, with massive left atrium, determined clinically
- B Extensive myocardial infarction, confirmed at necropsy
- C Chronic cor pulmonale secondary to pulmonary emphysema, confirmed at necropsy

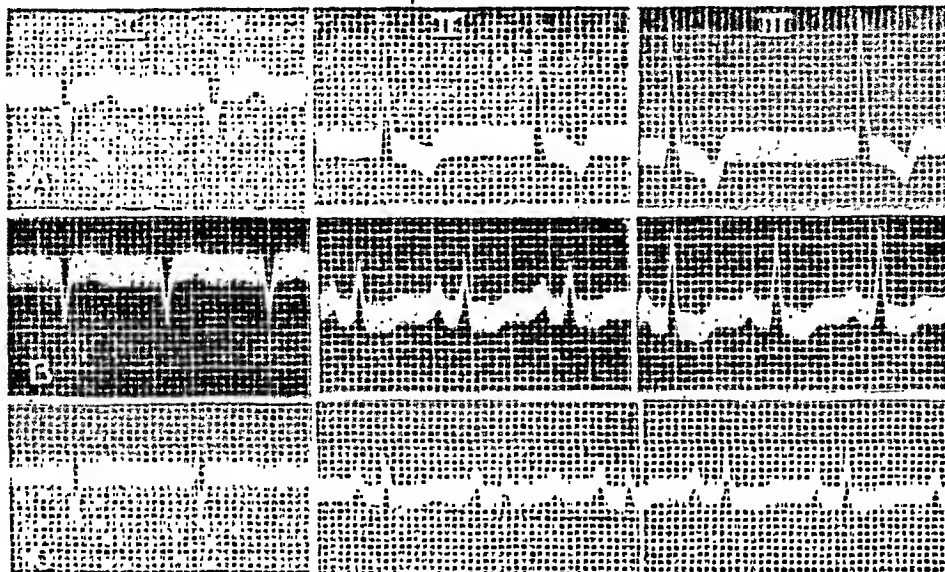


Fig 1.—Standard electrocardiograms (Leads I, II, and III) of Patients A, B, and C. Patient A was a 56-year-old white woman with rheumatic mitral stenosis and insufficiency, and probably aortic insufficiency. Patient B was a 42-year-old Negro with myocardial infarction. Patient C was a 42-year-old Negro with chronic cor pulmonale secondary to pulmonary emphysema. All three patients were in heart failure and were taking digitalis at the time the records were made. The diagnoses of Patients B and C were corroborated at necropsy.

The point illustrated is that widely different anatomic diseases can give very similar electrocardiograms. This, of course, is not new. But a more detailed electrocardiographic study of patients similar to these will demonstrate that deviation of the electrical axis in these three patients was caused by three distinct mechanisms, even though all might be spoken of as showing "right ventricular preponderance."

Studies on Patient B will be considered before the other two.

Right Axis Deviation With Infarction of the Left Ventricle.—Patient B showed an electrocardiographic pattern in standard leads which we have encountered in twenty-three patients in a random search. In fifteen of these, the extremity and six precordial potentials were recorded using the indifferent electrode of Wilson and associates,¹¹ in five, the hearts were available for section by the method of Kossman and de la Chapelle.²¹

From the special leads of this patient (Fig. 2), the cause of the right axis deviation was easily ascertained. The right arm (V_R) was almost at zero potential instead of the usual negative, and the left arm (V_L) was distinctly negative. Precordial Lead V_5 simulated Lead V_L . This suggested that both were semi-direct leads from the cavity of the left ventricle.

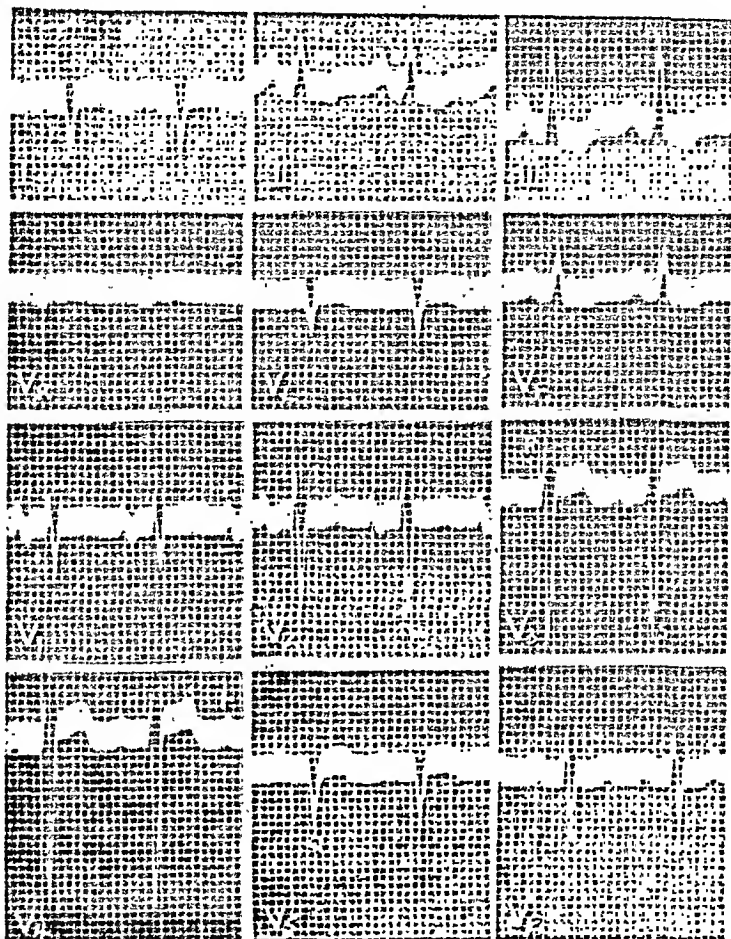


Fig. 2.—Patient B, myocardial infarction. Standard leads (I, II, and III) and extremity potentials (V_R , V_L , V_F) were recorded at normal string sensitivity (1 mv. = 1 cm.); the precordial potentials (V_1 , V_2 , V_3 , V_4 , V_5 , V_E) were recorded at half-normal string sensitivity (1 mv. = 0.5 cm.). Leads V_1 to V_5 were made at the standard precordial points; Lead V_E was recorded from the tip of the ensiform cartilage. The extremity and precordial leads were made with the indifferent electrode described by Wilson, Macleod, and Barker.¹¹ Time lines occur every 0.04 second.

The negativity and similarity of QRS in Leads I, V_L , and V_5 , and the low potential of QRS in Lead V_R , are to be noted.

At necropsy (Fig. 3), five days after the curves were recorded, there was found an extensive healed infarct extending from the apex for more than 6.0 cm. toward the base. Its circumferential and transmural extent was relatively less as it approached the base. At the apex the entire septum was involved, but toward the base the lesion in this structure was limited to its anterior half. In most places its entire thickness was involved, although small islands of muscle were preserved as was a subendocardial layer.²² There was extensive mural thrombosis, especially at the apex, and the anterior wall close to the septum bulged slightly. The right ventricle was not involved. The infarct

resulted from thrombotic occlusion of the anterior descending branch of the left coronary artery. Although the lesion was extensive, it was clear that the remaining left ventricular muscle was in excess of right ventricular muscle. However, actual weights were not determined.

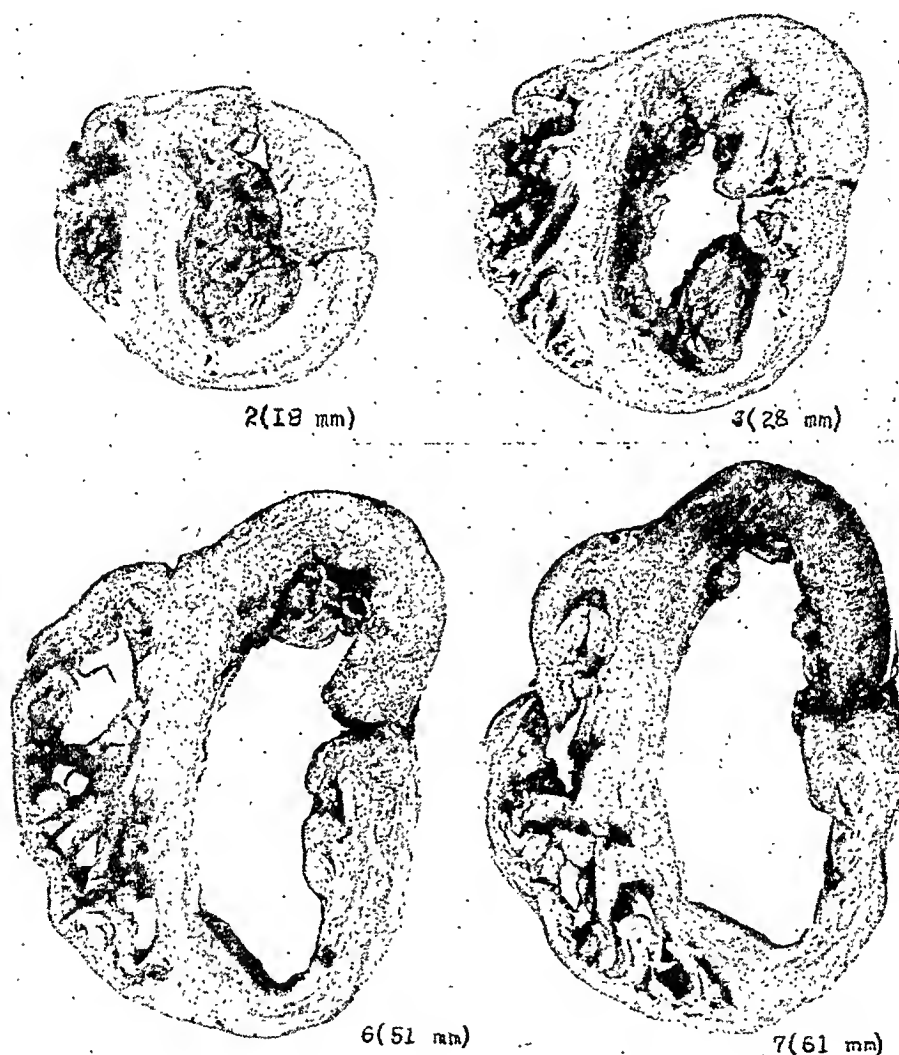


Fig. 3.—Patient B. Transverse sections 2, 3, 6, and 7 of the heart are shown. The basal side of each section is visible, with the anterior wall below and the left ventricle on the observer's right. The figures in parentheses indicate the level from the apex of the heart in millimeters.

Healed infarction is visible as the lighter areas in the septum, and in the anterior and lateral walls of the ventricles, mottled with small islands of remaining muscle. Thinning of these structures, mural thrombosis on the left, and slight bulging (aneurysm) anteriorly can be seen. The interlacement of trabeculae which make up the relatively normal right ventricular free wall are to be noted for later reference.

From the electrocardiograms of this and other patients in the series, it was evident that the right axis deviation was not due to a shift of the center of gravity of the heart, but rather was the result of the infarct being oriented with respect to the left arm. Any change in potential of the right arm from the normal probably resulted from the loss of left apical components directed downward,

which presumably contributed to its negativity before infarction occurred. The pattern displayed in the standard leads might be expected in a hypersthenic individual with a heart rotated in a counterclockwise manner in greater degree around its anteroposterior than around its long axis.

It was concluded from the group studied that preponderance of the right ventricle as a result of extensive necrosis of the left ventricle was a theoretical concept which probably does not occur.

Right Axis Deviation With Mitral Stenosis.—The teleroentgenogram (Fig. 4) of Patient A, who clinically was a case of rheumatic mitral stenosis and insuf-

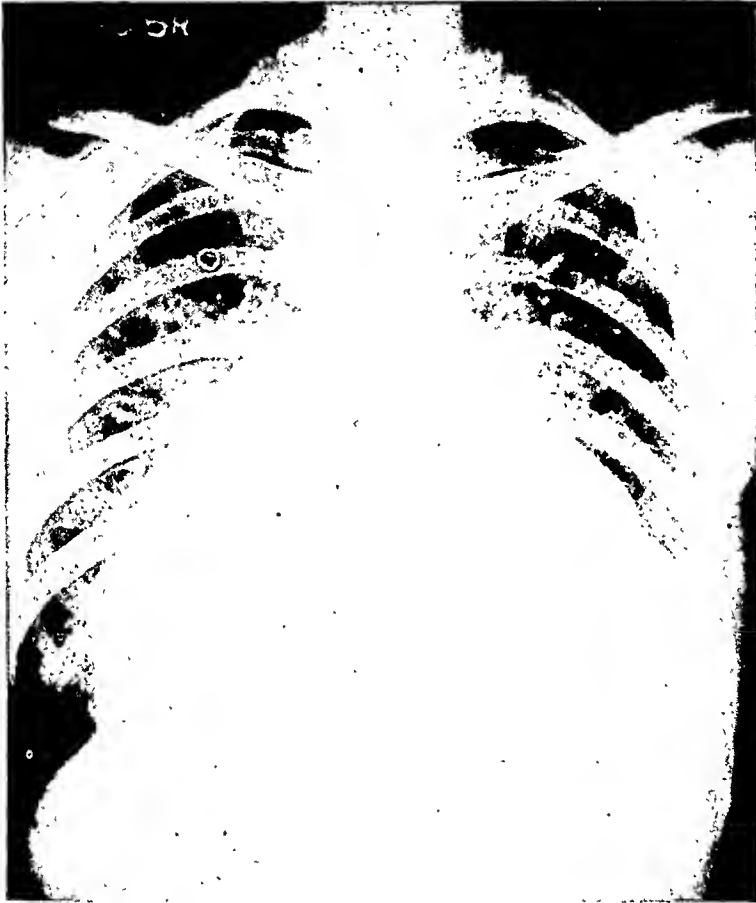


Fig. 4.—Patient A, rheumatic mitral stenosis, mitral insufficiency, and probable aortic insufficiency. Teleroentgenogram made within a short time of the electrocardiograms shown in Fig. 1. The massive size of the heart, filling of the cardiovascular angle on the left, and shadow of the left atrium on the right are the points of interest.

ficiency and possibly aortic insufficiency, showed a greatly enlarged heart of globular shape and displayed a shadow of a huge left atrium on the right border.

The extremity potentials (Fig. 5) revealed that the right axis deviation was the result of the left arm being more negative than the right, although both extremities were negative. The lead from the left leg was similar to leads from

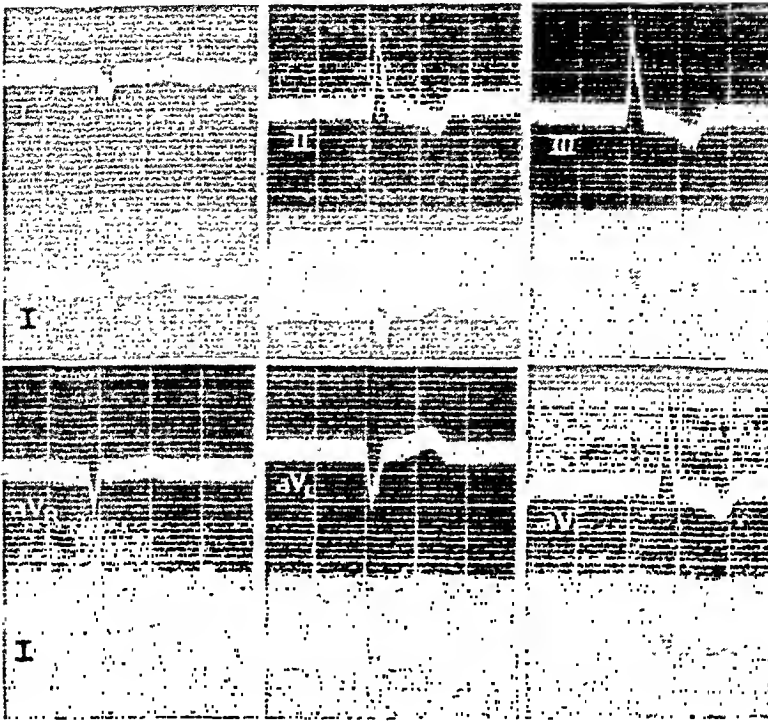


Fig. 5.—Patient A. Standard leads (I, II, and III) and augmented extremity potentials (aV_R , aV_L , aV_F) recorded simultaneously with Lead I, all at normal sensitivity of the string. The cause for right axis deviation is obvious from the greater negativity of the left arm (V_L) than the right (V_R) during inscription of QRS. The Q and late R in Lead V_F , and the similarity of this lead to Leads II and III are caused by the effects of the dependent left ventricle on the left leg. Time lines occur every 0.2 second.

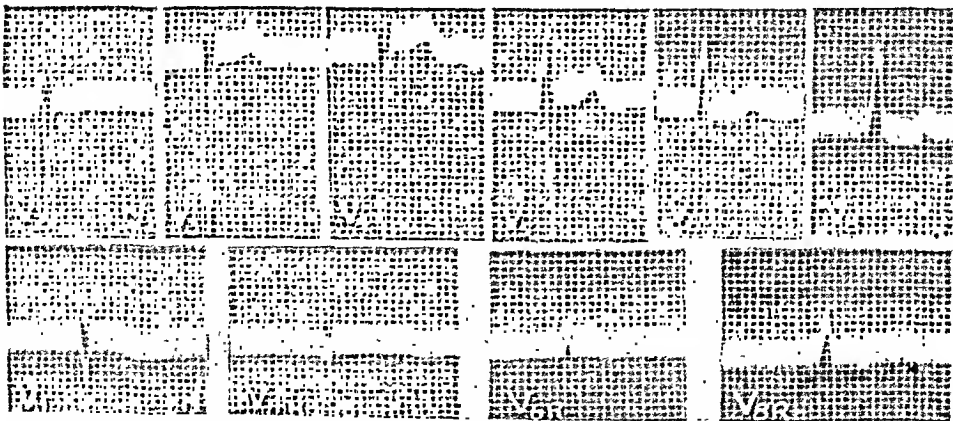


Fig. 6.—Patient A. Precordial potentials V_1 to V_6 were from the usual thoracic points. Lead V_8 was made with the exploring electrode in the left midscapular line at the same horizontal level as chest point 4. Leads V_{4R} , V_{6R} , and V_{8R} were recorded from the right side of the thorax, the arabic subscript indicating the position of the electrode as on the left side of the precordium. The records in the upper part of the figure were made with the string at half-normal, those in the lower part at normal sensitivity. Time lines occur every 0.04 second.

The small R wave in leads from the right side of the thorax, and its absence in Lead V_4 , are to be noted. In Lead V_8 the R wave is "transitional."

the far left side of the precordium, indicating a vertical electrical position of the heart.²³ On investigating the precordial leads (Fig. 6), it was observed that a late R wave was not to be found on the right side of the precordium (Leads V_1 to V_5), as might be expected if such a deflection was caused by right ventricular hypertrophy. Actually, the R was quite small in these leads and even absent in Lead V_4 , possibly due to a high position of the electrode on the chest. A late R wave, such as is usually obtained over the left ventricle, was recorded only when the exploring electrode was in the left midaxillary line (Lead V_6). Further, a similar late deflection was encountered with continued exploration of the back as far around to the right as the midaxillary line (Lead V_{6R}). Only when a lead from the right midclavicular line was made (Lead V_{4R}) did the curve obtained again resemble those found at other points on the front of the precordium.

With the anatomic knowledge that a large right ventricle makes up the greater part or all of the anterior surface of the heart, these electrocardiographic findings suggest that the anterior chest wall between the axillary lines was principally in the electrical field of the right ventricle and that the posterior chest wall between these lines was in the field of the left ventricle. Comparable lines of transition in a normal subject are on the average between the midclavicular line and the left sternal edge anteriorly⁹ and, though quite variable, usually in the region of the dorsal spine posteriorly. This would mean that in Patient B considerable rotation of the heart in a clockwise manner around its long axis had occurred. To be noted particularly is that, although this right ventricle was distinctly hypertrophied (by inference and from x-ray findings), the R wave in its electrical field was early and small. It has been customary to ascribe such a finding to concomitant extensive hypertrophy of the left ventricle. Some enlargement of this chamber certainly existed but, as will be seen, it was probably not the factor responsible for the small R wave in leads from the front of the thorax.

To investigate the matter further, endocardial electrocardiograms were recorded in several patients after introduction of an electrode into the right atrium and right ventricle by way of an antecubital vein. The methods will be detailed elsewhere.²⁴

In a normal subject with a vertical heart, the electrode at Points 1 and 2 as shown on the x-ray film (Fig. 7) was in the right atrium. At the remaining points (3 to 7), it was in the right ventricle. The location of the electrode when Lead V_3 was recorded from the chest is shown for comparison.

The standard and extremity leads, precordial Leads V_1 , V_2 , and V_5 , and an intracardiac lead with the electrode in the right ventricle at Point 3, showed the following points of importance (Fig. 8): (1) Lead aV_R simulated Lead V_{RV3} (cavity of the right ventricle). (2) Leads V_1 and V_2 were similar to the intraventricular lead, although the R was a little taller in Lead V_2 . The R waves and the S waves were a little later in the chest leads than in the cavity leads. (3) The intraventricular lead began with an R wave which was presumably the result of early activation of the left side of the interventricular septum. (4) The

T wave was negative with the electrode in the cavity, and positive with the electrode on the precordium.

Most noteworthy is that the R wave in a lead from the right ventricular cavity was slightly earlier than an R wave recorded from the right side of the precordium. Further, in Lead V_2 this deflection had two peaks. This and other

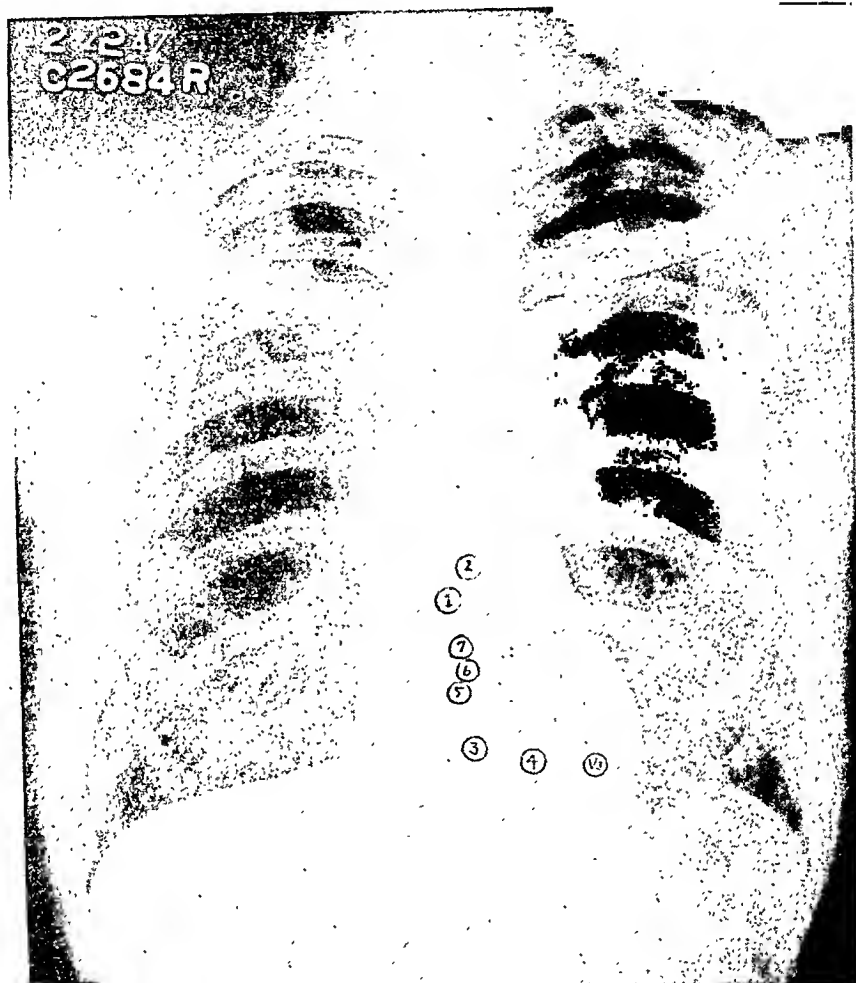


Fig. 7.—X-ray film of a patient with a normal heart showing various locations of an intracardiac electrode as projected on the thoracic surface by the central ray of the fluoroscope. At Points 1 and 2 it was in the right atrium; at Points 3 to 7 it was in the right ventricle. The location of Lead V_3 on the chest is shown for comparison.

This and subsequent similar x-ray films were made by putting a small metal marker on the chest directly over the intracardiac electrode during the catheterization. A teleroentgenogram was made immediately after completion of the electrocardiographic studies with the subject recumbent, as during the electrocardiographic studies, and again standing. Differences between the two were slight in this patient. The teleroentgenogram shown was made with the patient standing.

available data²⁴ suggest that this deflection has a dual origin in a precordial lead from the right side: first, it is caused by early excitation of the left side of the interventricular septum; and second, by passage of the action current through the free wall of the right ventricle. Any differences in the R wave of intracardiac

and extracardiac leads should be due to components contributed by the free wall of the right ventricle.*

In this and in other normal subjects studied, the amount contributed to QRS by the free wall was small. At least two explanations can be given: (1) the voltage developed across the free wall of the right ventricle is in truth small; and (2) the voltage developed across the free wall is slower than the simultaneous development of negativity of the cavity. One reason for believing the first to be correct will be discussed later.

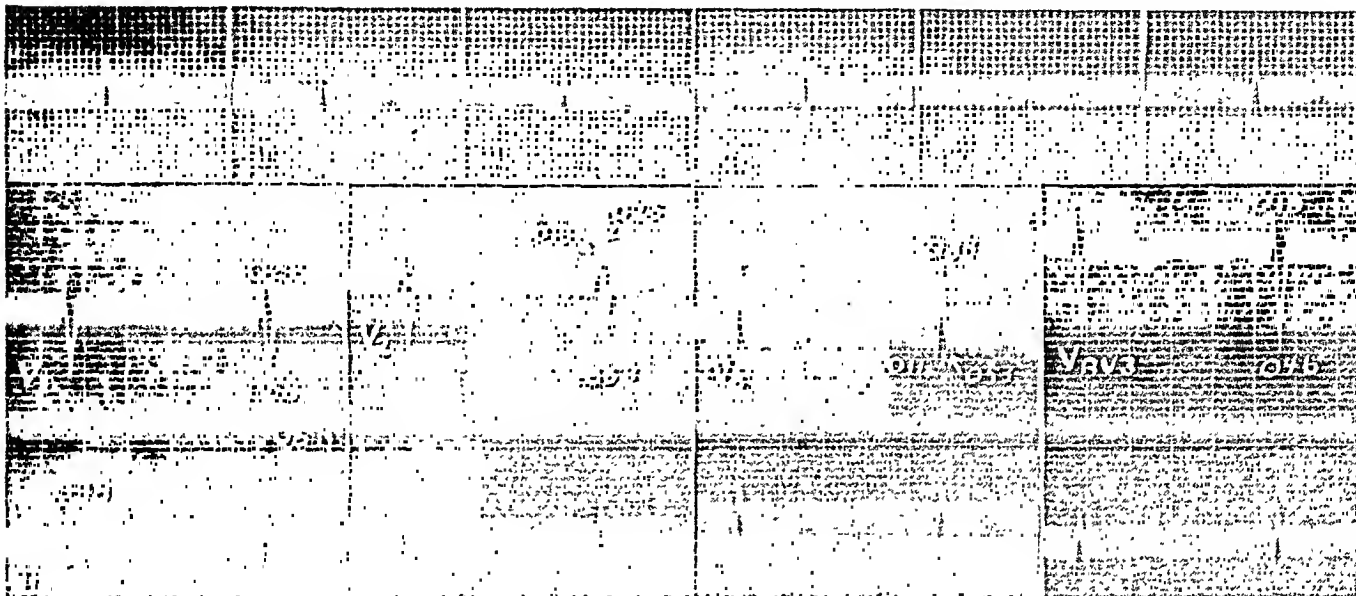


Fig. 8.—Patient with normal heart whose x-ray film is shown in Fig. 7. Leads I, II, III, aVR, aVL, and aVF were recorded at normal sensitivity. Leads V₁, V₂, V₃, and V_{RV3} (right ventricular cavity with electrode at Point 3, Fig. 7) were recorded at half-normal sensitivity simultaneously with standard Lead II at slightly less than normal sensitivity of the string. The figures on the curves represent the time in seconds of the deflections over which they are written with reference to the beginning of QRS in Lead II. The timelines in the upper row occur every 0.04 second; in the lower two, every 0.2 second.

To be noted are the similarity of Leads V₁, V₂, and V_{RV3} except for the direction of the T wave.

To return to the problem at hand, the question that arises next is how much does the free wall of the hypertrophied right ventricle in mitral stenosis contribute to the R wave? In this study another patient (W. F.) with rheumatic mitral stenosis, mitral insufficiency, and auricular fibrillation was used. The heart on x-ray study (Fig. 9) showed the characteristic shape, with prominence of the pulmonary artery or its left branch²⁵ in the middle arc. The left atrium was enlarged posteriorly. The standard leads (Fig. 10) showed an angle alpha of approximately +60°. The mean potential of the left arm was approximately zero, the electrical position was semivertical and hence QRS was upright in Lead I. Despite good clinical evidence of right ventricular hypertrophy, there were no R waves which were late or large in leads from the right

*Size of the R wave is not a reliable measure of the thickness of the underlying ventricular wall. Time of the deflection is perhaps more so, and most reliable of all is the size of the RS deflection, which in direct leads is a measure of the total electromotive force developed across the wall from endocardium to epicardium. But even this measurement is unreliable in indirect leads where the effect of surrounding conducting tissues, of the contralateral ventricle, and of perhaps other variables are unknown.

side of the precordium (Fig. 10, Leads V_{4R} to V_4). A small Q and late R were encountered in Lead V_5 , and similar curves were obtained in leads from the left chest and back as far over to the right as the midscapular line. Beyond this, on the right the curves displayed all downward direction of QRS similar to that shown in Lead V_{4R} . The small size of R in curves obtained from the front of the thorax and its absence in Lead V_3 were similar to the findings in Patient A. Also of interest was the late small positive deflection in Lead V_2 , which possibly arose in the pulmonary conus.²⁶

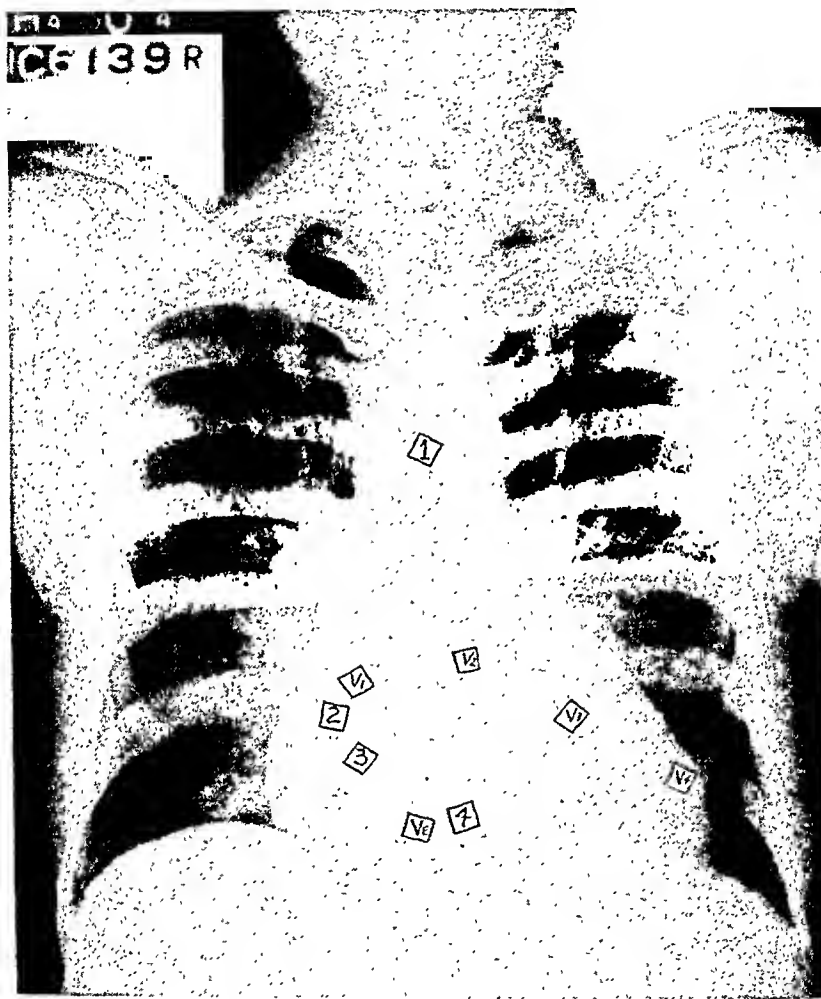


Fig. 9.—Patient W. F., rheumatic mitral stenosis and insufficiency. Teleroentgenogram made just after cardiac catheterization. Numbers on the heart shadow have the same significance as in Fig. 7. The patient was a 42-year-old white man with auricular fibrillation but not in heart failure. The characteristic shape of the heart is to be noted. On fluoroscopy there was marked enlargement of the pulmonary conus and left atrium, with some calcification in the wall of the latter. The left ventricle showed some enlargement posteriorly.

Potentials were obtained from both the right atrial and right ventricular cavities. While the electrode was in the inferior part of the right ventricle (Point 4 in Fig. 9), another electrode was placed directly over it on the precordium, and leads were recorded simultaneously with two string galvanometers (Fig. 11).

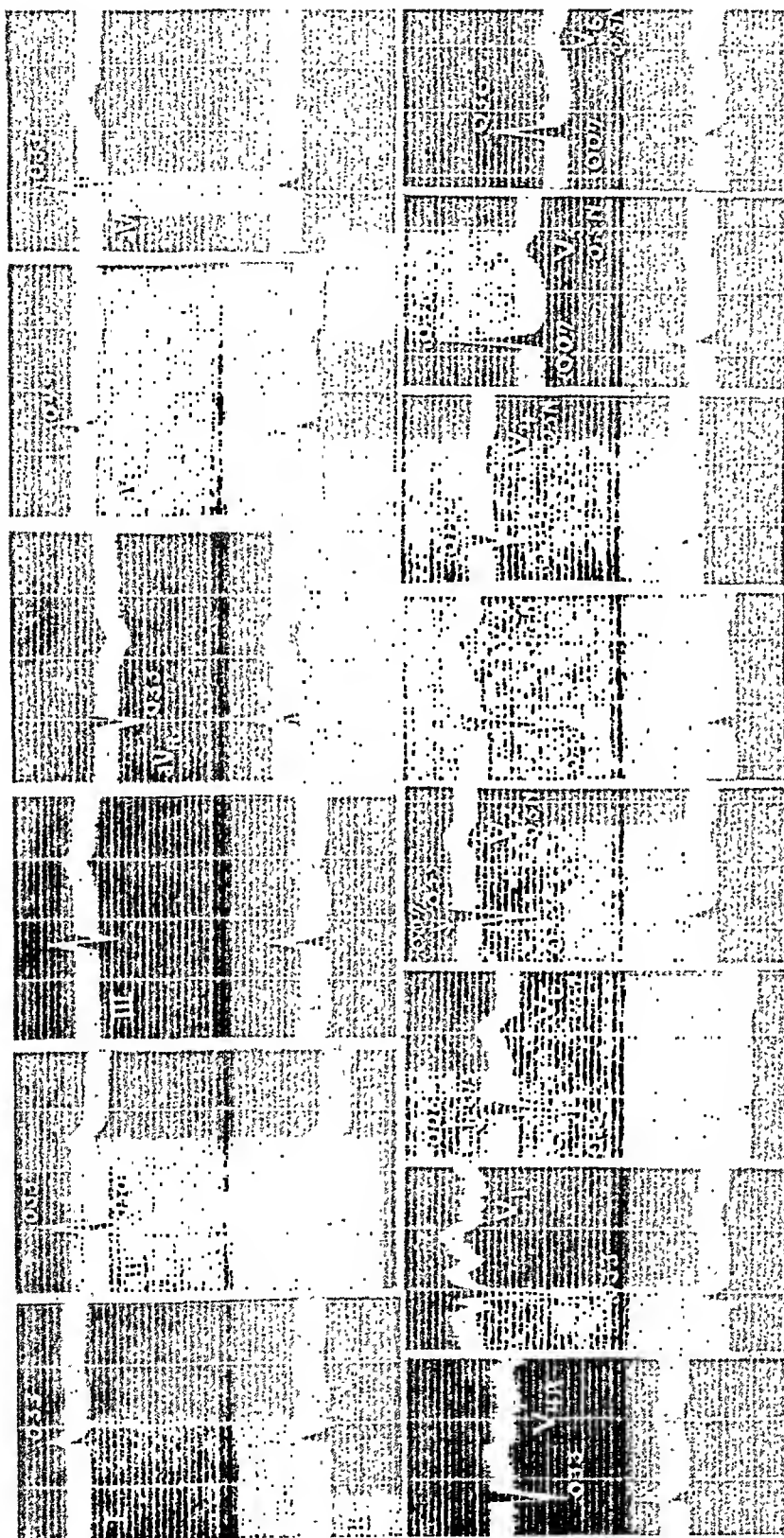


Fig. 10.—Patient W. F. Standard leads (I, II, and III), augmented extremity potentials (aV_R , aV_L , aV_F), and precordial leads (V_1 , V_2 , V_3 , V_4 , V_5 , V_6) recorded simultaneously with standard Lead I. Symbols and figures have the same significance as in previous illustrations. Leads V_7 , V_8 , and V_9 (not shown) were similar to Lead V_6 . Lead V_{10} (not shown) was similar to Lead V_4R . All leads in the upper row, and Leads V_4R and V_1 in the lower row, were recorded at normal sensitivity of the string; others at half-normal. Time lines occur every 0.2 second.

Both records were made with string sensitivity identical (0.6 normal). Quantitative differences were limited to a slightly smaller R wave and an inverted T wave in the lead from the cavity. Compared with the beginning of QRS in Lead I, the peak of R in the cavity lead was 0.004 second later, and the two peaks of R in the precordial lead were 0.006 and 0.015 second later, respectively. The opposite direction of the T wave in the cavity and precordial leads was probably caused, as in normal subjects,²⁴ by a gradient in the duration of the excited state across the free wall of the right ventricle such that activity was of longer duration on the endocardial surface.

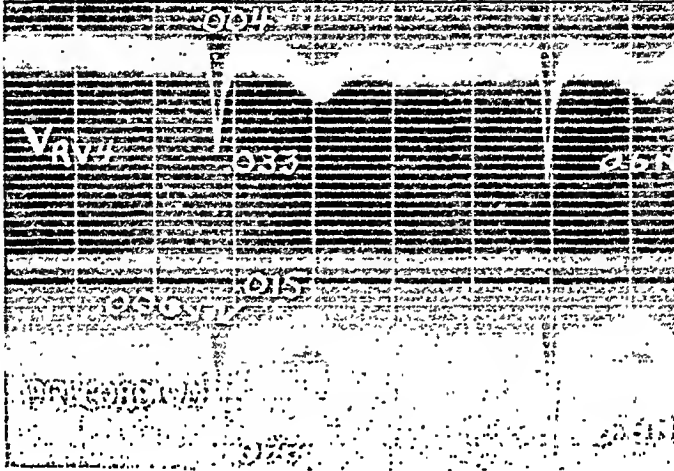


Fig. 11.—Patient W. F. Simultaneous records at identical string sensitivities (0.6 N) from a point inside the right ventricle ("V_{RV4}," upper string, electrode located at Point 4, Fig. 9), and from a precordial point directly over it ("Precordium," lower string). Figures indicate time in seconds between the deflection concerned and the beginning of QRS in Lead I.

To be noted are: similarity of the leads; the double peak of R in the precordial lead; and the opposite direction of the T waves.

It might be assumed that the contribution of the free right ventricular wall to QRS was small, and the R wave of the precordial lead not too different from the R wave of the cavity lead by virtue of dilatation. Although the patient was receiving digitalis, he displayed no evidence of congestive heart failure at the time the records were made. Dilatation of the right ventricle was not present.

It would appear from these data that the lateral wall of the right ventricle contributes little to the extrinsicoid deflection or R wave in leads from the right side of the precordium, and that this statement is true when the right ventricular wall is thickened as a result of mitral valvular disease with stenosis. Further, clockwise rotation of the heart about its long axis, as illustrated in Patients A and W. F., is apparently not extensive when there is mitral stenosis even when right ventricular hypertrophy is considerable, as in Patient A. A possible explanation is that the concomitantly enlarged left atrium prevents such rotation to any extreme degree.

Right Axis Deviation in Chronic Cor Pulmonale.—Patient C showed chest leads which differed from those seen in the records of the patients with mitral

stenosis. A lead from the right sternal edge, though of very low voltage, displayed a Q, a late R, and an inverted T. In the only other precordial curve available, Lead V_6 , there was a small R, deep S, and positive T. No other special leads were available on this patient before death. At necropsy, the right ventricle was abnormally thick but not thicker than the left, even though the R wave, measured from the beginning of QRS, was later on the right than on the left by approximately 0.01 second.

Another patient, A. K., with advanced chronic cor pulmonale, was available for detailed study. The standard leads (Fig. 12) displayed a deep S wave in Lead I; Leads II and III were low and bizarre. From the extremity potentials the electrical position of the heart was indeterminate because of the low, vibratory nature of Leads aV_L and aV_F .

Lead aV_R was similar to Lead V_1 (Fig. 13) and to all the leads recorded to the right of the midline as far around the back as the midscapular line (Lead V_{8R} , not shown). The intracavitary potential of the right atrium (not shown) had an identical contour.

Notable in the precordial leads which were recorded simultaneously with a lead from the cavity of the right ventricle (Fig. 13) were: their similarity to those of Patient C; the abrupt change in the curve as soon as the midline was crossed (Lead V_E , not shown, was similar to Lead V_1), although anatomic considerations would indicate that certainly precordial Points 2 and 3 and probably 4 were in the electrical field of the large right ventricle; and the small R wave and prominent S wave without a Q wave, such as are seen over the normal right ventricle, even in a lead as far to the left as Lead V_7 (which was similar to Lead V_6 , Fig. 13). The peak of the R was earlier in Leads V_2 , V_3 , and V_4 than in Leads V_5 to V_7 (0.004 second and 0.025 second, respectively, measured from the beginning of QRS in Lead I). On the other hand, leads from the right side and back of the thorax (V_1 , V_{4R} , V_{6R} , and V_{8R}) and from the cavity of the right atrium displayed a Q, a late large R, and an inverted T. In all these leads, with one exception which will be discussed, the peak of Q and the peak of R occurred, respectively, at an identical time; namely, 0.016 and 0.050 second after the beginning of QRS in Lead I.

When an electrode was placed on the precordium directly over the intracardiac electrode (Fig. 14) and leads were made simultaneously (Fig. 13, " V_{RV3} " above and "Precordium" below), the curves did not differ in general contour, although there were differences compared with the records of the case with mitral stenosis (Fig. 11) similarly made. The R wave in the endocardial lead consisted of three different peaks, only the first of which preceded the peak of R in the chest lead. Although the relative size of R and S was approximately the same in both records, the RS deflection measured approximately 18 millivolts in the cavity lead compared with 3.0 millivolts in the lead from the precordium. The S wave in the cavity lead preceded the initial peak of S in the chest lead by a small interval (0.005 second), but the second peak of S in the latter was 0.023 second later, and was simultaneous with the R wave in leads from the right side of the thorax. This indicates that the first peak of S resulted from the comple-

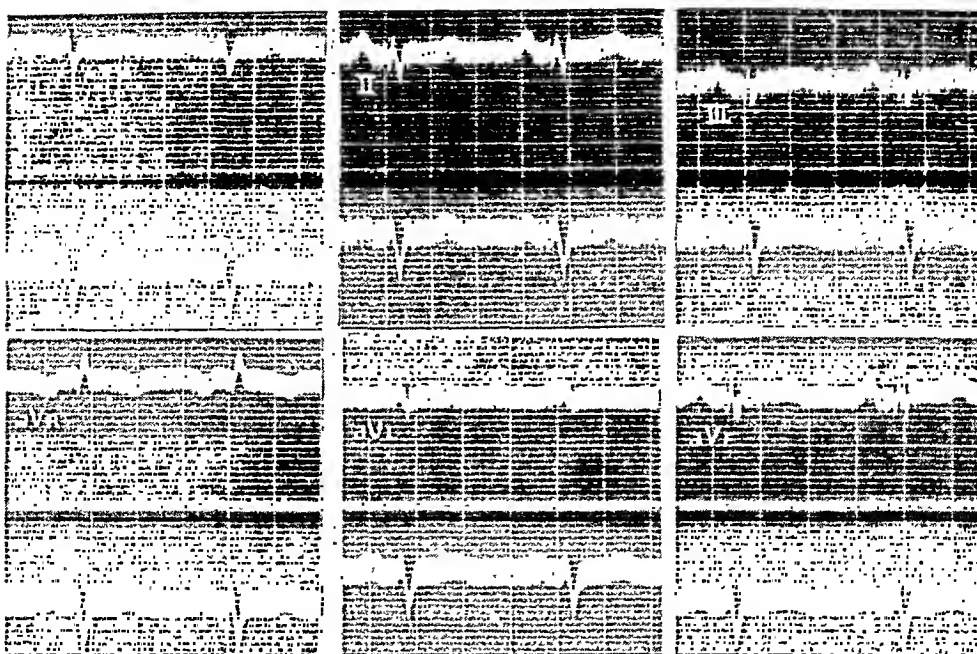


Fig. 12.—Patient A. K., a 57-year-old white man, who had been a coal miner in youth and who was regarded as having chronic cor pulmonale for five years before the electrocardiograms were recorded. He was taking digitalis. The standard leads (I, II, III) and augmented extremity leads (aV_R , aV_L , aV_F) were recorded simultaneously with Lead I. Time lines, 0.2 second.

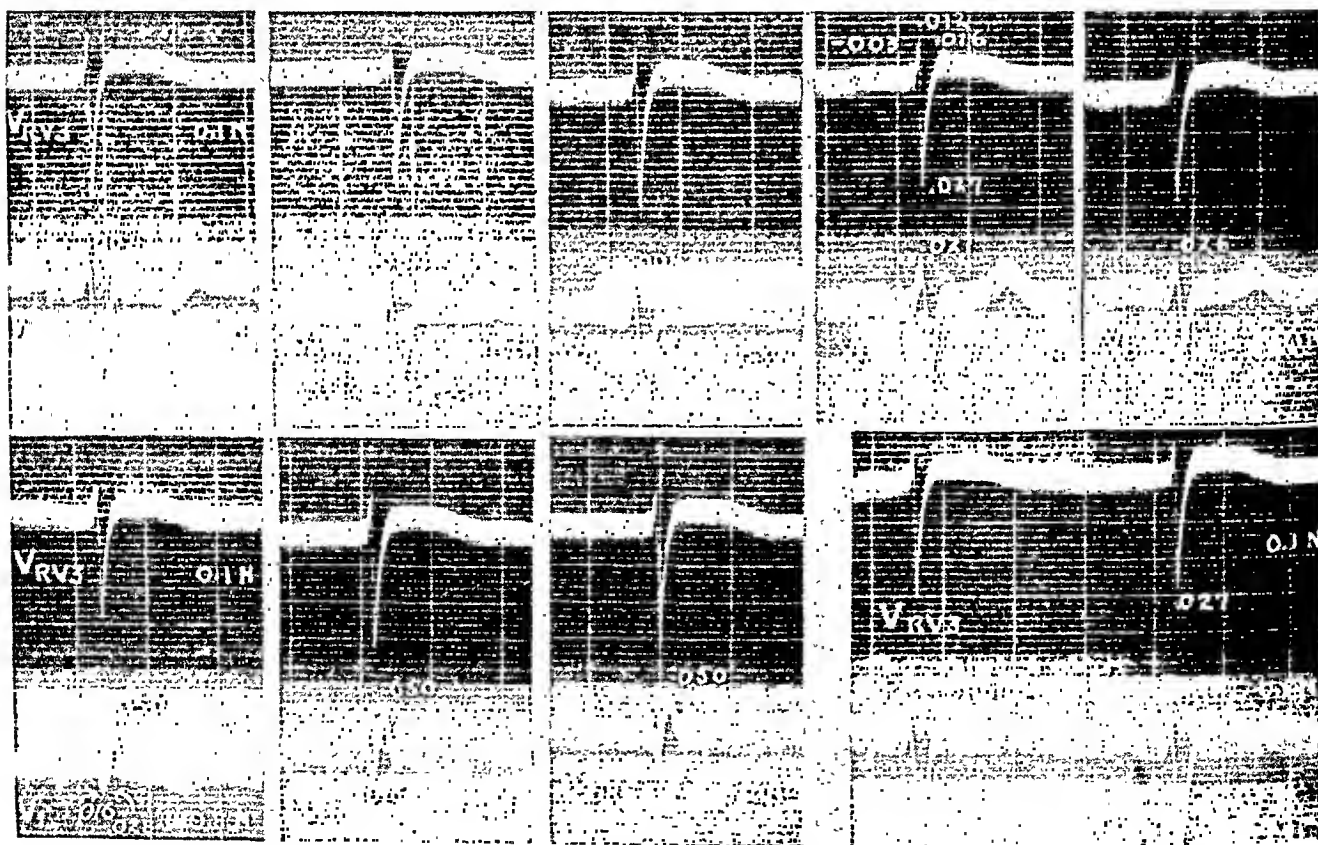


Fig. 13.—Patient A. K. Right intraventricular Lead V_{RV_3} (upper string at 0.1 N sensitivity) from Point 3 in ventricle (see Fig. 14) recorded simultaneously with various precordial leads at varying string sensitivities as indicated. Leads V_E , V_{SR} , and a lead from within the right atrium (Point 5, Fig. 14) were similar to Lead V_{GR} . Figures indicate the time in seconds of the deflection concerned from the beginning of QRS in Lead I. The R wave of the intraventricular electrocardiogram shows three distinct peaks. In the lower right hand corner a lead from the ventricular cavity (V_{RV_3}) was recorded with a lead (precordial) from a point on the chest directly over the intracardiac electrode. Time lines, 0.2 second.

tion of activity across the underlying ventricular wall while the second peak was a distant event, resulting from excitation reaching the epicardial surface of the contralateral ventricle. Since the precordial lead as taken was almost definitely in the electrical field of the right ventricle, the contralateral ventricle in this instance was the left ventricle.

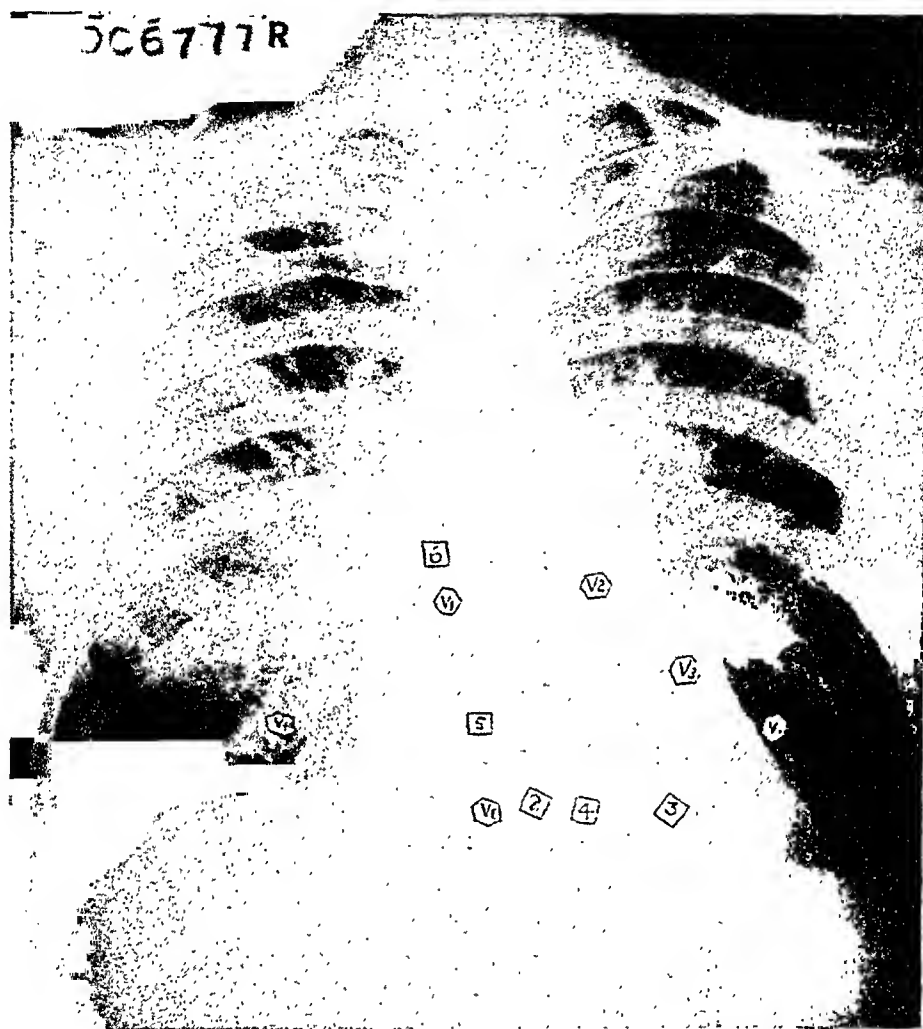


Fig. 14.—Patient A. K. Teleroentgenogram made with the patient standing, lead markers having been placed at points on the chest from which precordial leads were taken (hexagonal figures) and over the locations from which endocardial leads were made (square figures). To be noted are: the location of Point 3 at the apex of the right ventricle; the high location of Leads V_1 and V_2 as opposed to Lead V_E ; and the location of Lead V_{6R} (just visible in lower left hand corner of figure). At Point 6, the intra-cardiac electrode was in the superior vena cava; at Point 5, it was in the right atrium; at the others, it was in the right ventricle.

The shape of the heart and the length of the thoracic cavity are to be noted.

These data, when interpreted in the light of what has been presented up to now, make it necessary to come to the following conclusions. The left ventricle, and not the thickened right ventricle, was responsible for the late intrinsicoid deflection encountered in leads from the right side of the thorax in this case of chronic cor pulmonale. It appears that there was extreme clockwise rotation of the heart around its long axis to an even greater degree than in the patients with mitral stenosis. The right ventricle was rotated far to the left, and a transi-

tional zone occurred over a wide area in the left axilla. The actual change from right ventricular to left ventricular electrical fields was posterior rather than in the left parasternal line anteriorly as in normal subjects. Further, the transition zone from left ventricle to right ventricle, instead of being posterior, was in the vicinity of the midsternum anteriorly.

At first glance this seems incredible from an anatomic point of view. Studies that have been made with angiography are not of much help because of the difficulty encountered in visualizing the left ventricle. Examination of a good heart model will show that it is entirely possible, particularly if, in addition to the clockwise rotation about the long axis of the heart viewed from the apex, there is also considerable similar rotation about an anteroposterior axis and transverse axis viewed from the left. It is believed that such unusual degrees of rotation can occur in chronic cor pulmonale because the voluminous lungs make it possible by greatly increasing the anteroposterior and long diameters of the thorax. Further, there is no great enlargement of the left atrium posteriorly, as in mitral stenosis, to interfere with rotation about the long axis.

It is probable that the left ventricular curve obtained in Lead V_1 was not the result of a direct relationship of the exploring electrode to the surface of the left ventricle, but rather was indirect through the intervening right atrium. It is surmised that this latter chamber which is enlarged in cor pulmonale, particularly if heart failure has occurred, may actually overlap the posterior basal part of the left ventricle. A point in support of this is that an intra-atrial lead in the case under consideration displayed a curve identical with that obtained from the right sternal edge.

It is probable that the peak of the Q wave in Lead V_1 was not created in the way that a Q wave usually is when an electrode is over the left ventricle. It was discovered that the last part of the Q was simultaneous with the peak of the S wave in the cavity of the right ventricle. It is possible, therefore, that it was created in part as a result of Lead V_1 being a semidirect lead from the cavity of the right ventricle by virtue of the electrode being close to the auriculo-ventricular orifice of this chamber. This explanation is plausible if the anatomic considerations given before are accepted. Further, in Lead V_{4R} , and in others to the right, the peak of Q was simultaneous with the peak of R in the cavity lead from the right ventricle, while its ascending limb was slurred at a time when the peak of S in the cavity lead was written. In these leads, then, only part of the Q wave was created in the manner described for Lead V_1 .

If this explanation of the origin of the Q wave in Lead V_1 is correct, this deflection becomes unreliable as an index of beginning excitation of left ventricular endocardium subjacent to the electrode (see footnote, † p. 310). However, it may be reliable in other leads made at lower levels and more posteriorly on the right, in which the peak of Q was simultaneous with the peak of the R wave in the cavity leads (about 0.016 second from beginning of QRS in Lead I).

RIGHT AXIS DEVIATION IN TETRALOGY OF FALLOT

A patient, M. F., 11 years of age, with a clinical diagnosis of tetralogy of Fallot, was explored electrocardiographically, although cavity potentials were not recorded. The electrocardiograms (Fig. 15) showed the usual right axis deviation in the standard leads. The special leads were strikingly similar to those in the case of chronic cor pulmonale just presented (Patient A. K.). Of particular interest were: the Q and late R in Leads aV_R and aV_F , although the T wave was negative in the first and positive in the second; the similarity of Leads V_2 to V_8 (left midscapular line) with a relatively small R, except in Lead V_4 , and a deep S; the similarity of all leads from the middle of the sternum to the right as far as the right midscapular line (Lead V_E to Lead V_{8R}), and the likeness of these to Leads aV_R and aV_F ; and the abruptness of the change between Leads V_2 and V_E .

The x-ray films were not unusual, although an angiocardigram* made in the left anterior oblique position showed a posterior left ventricle, free of contrast media; an aorta, pulmonary artery, and right ventricle filled as expected; and a persistent right aortic arch (Fig. 16). The considerable spaciousness of the retrocardiac space, and the right-sided aorta presumably facilitated clockwise rotation of the heart around its long axis.

The patient came to necropsy two days after the electrocardiograms were made following an unsuccessful surgical exploration. There was a tetralogy of Fallot with infundibular stenosis. The right ventricle ranged in thickness from 7 mm. at the apex to between 7 mm. and 10 mm. at the base. The conus just below the stenosis measured 6 mm. in thickness. The walls of the cavity, particularly in its apical four-fifths, were irregular, and were made up of thickened, closely packed trabeculae which, however, could easily be separated except at the base. The left ventricle was slightly thicker, and measured 11 mm. at the apex and 10 mm. at the base. Its endocardial surface, in contrast to that of the right ventricle, was relatively smooth throughout. Its wall was made up of solid muscle rather than of closely packed, interlaced and hypertrophied trabeculae.

Several facts stand out in this case. The free walls of the right and left ventricles were of almost the same thickness, yet the electrocardiograms displayed intrinsicoid deflections which appeared at widely different times on the two sides of the precordium (Fig. 15). Undoubtedly there were multiple causes for this, but one possible anatomic reason could hardly go unnoticed, namely, the different structure of the two chambers. If reference is made to Fig. 3, it will be seen that the right ventricular wall is made up of trabeculae which in places almost fill the cavity. The "wall" itself is made up of only the thinnest layer of what may be called "solid muscle," and this is probably even thinner in the distended living ventricle. No matter in which direction it is assumed that the trabeculae are stimulated, from the outside, from the center, or eccentrically, the total electrical effect of these trabeculae must be small.

*The authors are grateful to Dr. U. J. Roche for making this angiocardigram with the help of the radiologists at Lenox Hill Hospital, New York, N. Y.

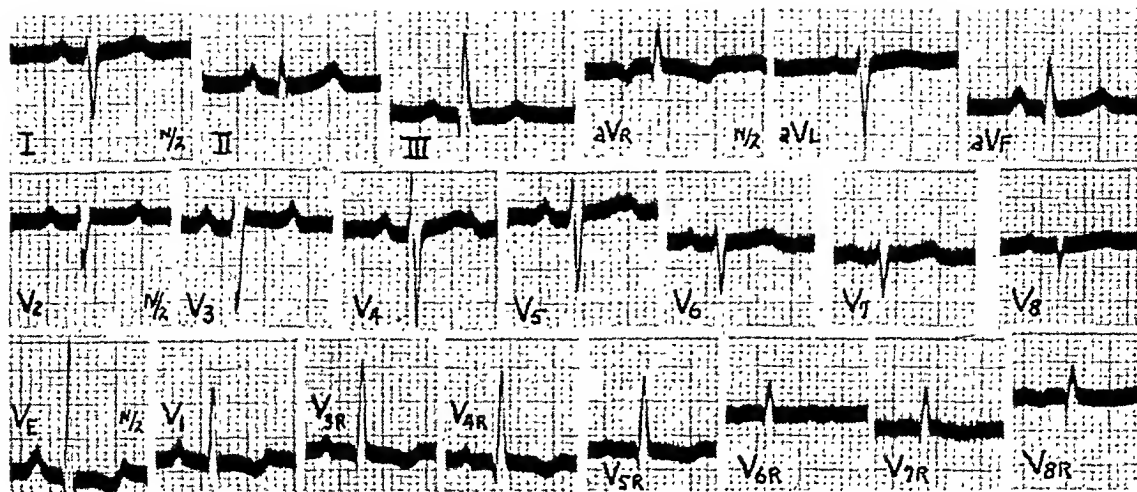


Fig. 15.—Patient M. F., with the tetralogy of Fallot. All leads were recorded at 0.5 N sensitivity of the oscillograph. Designation of leads is the same as in previous tracings. To be noted are similarity of leads in the second row to Lead aVL and to each other, and the similarity of the curves in the lowest row to Leads aVR and aVL, and to each other.

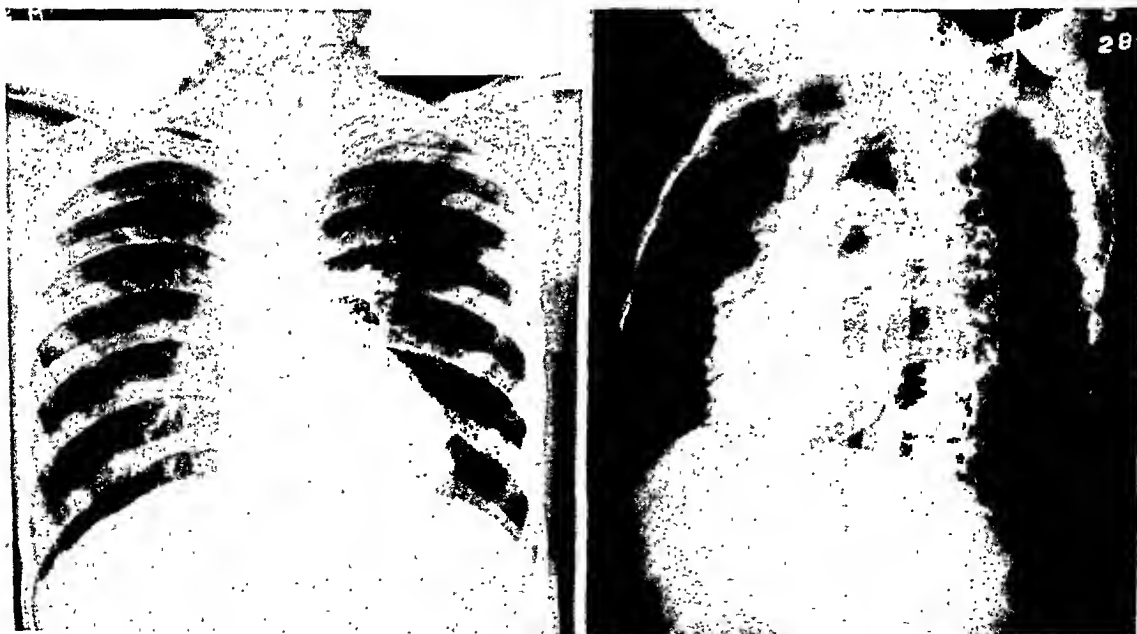


Fig. 16.—Patient M. F. Teleroentgenogram on left with barium in esophagus, and on the right an angiogram made with the patient in the left anterior oblique position. In the latter, the contrast medium is in the right ventricle, in the aorta, and in the pulmonary artery. The aorta is on the right. To be noted is the considerable distance between the heart and the spine posteriorly.

When there is hypertrophy of the chamber, as in the present case, there is merely an exaggeration of this situation, perhaps with some increase in the "solid" wall especially of the base, but the total electrical effect is theoretically still small if intraventricular conduction is unimpaired.

RIGHT AXIS DEVIATION AS A RESULT OF INTRAVENTRICULAR BLOCK WHEN THE QRS INTERVAL IS WITHIN NORMAL LIMITS

The electrocardiograms of Patient J. R. are shown in Fig. 17. This 59-year-old patient had arteriosclerotic and pulmonic heart disease with a dilated pulmonary artery, and pulmonic valvular incompetence³⁹ whenever he was admitted to the hospital in heart failure. However, x-ray films showed a large left ventricle as well as a long pulmonary arc (Fig. 18). The lungs were emphysematous. At the time the electrocardiograms were recorded the patient was taking digitalis.

The curves differed in several important respects when compared with those of Patient A. K. (Figs. 12 and 13). Deviation of the electrical axis to the right was not so marked. In Lead aV_R , the Q wave preceding the late R was deeper. The small R in Lead aV_L was preceded by a minute Q wave. This lead was similar to leads obtained from the left side of the precordium (V_5 to V_7). The ventricular gradient in the frontal plane was further to the left, possibly in part attributable to digitalis. The QRS interval was 0.094 second.

The thoracic leads differed quite markedly (Fig. 17). Leads V_1 and V_2 displayed an initial R wave of small size which was followed by a small S and a late large positive deflection which was splintered, so that there was actually an R' and R'' . Contours in Leads V_{3R} , V_{4R} , and V_{5R} were similar except that R'' could not be identified. Farther to the right, the R could not be seen but the R' (now really R) was late, though small, as far around as Lead V_{8R} . Continuing to the left, Leads V_8 , V_7 , V_6 , and V_5 showed a different contour with an early R, and a broad but similar sized S wave. A small Q was present in Leads V_5 , V_6 , and V_7 which can be seen better, at least in Lead V_5 , in Fig. 19.

In Leads V_3 and V_4 there were features simulating both dominant types of curves suggesting that these leads were from transitional zones.

It would appear that rotation, such as was present in the prior two instances, was not present in this case (Fig. 18). The small Q and rapid R in Leads V_4 , V_5 , and V_6 suggest that these deflections were part of the levocardiogram, and that the broad S was in some way caused by events on the right side, or at any rate by electrical forces proceeding away from the left side.

The potential of the right atrium during ventricular excitation consisted of an initial small positive deflection, a deep negative deflection, and a late broad positive deflection (R') and an inverted T wave. The ventricular cavity (Figs. 19 and 20), explored at several levels, displayed deflections of the same nature throughout except when the electrode was against the endocardium so as to cause displacement of the S-T segment. The "average" potential consisted of an R wave, usually notched, and a deep S with several smaller notches on its descending limb (Fig. 19).

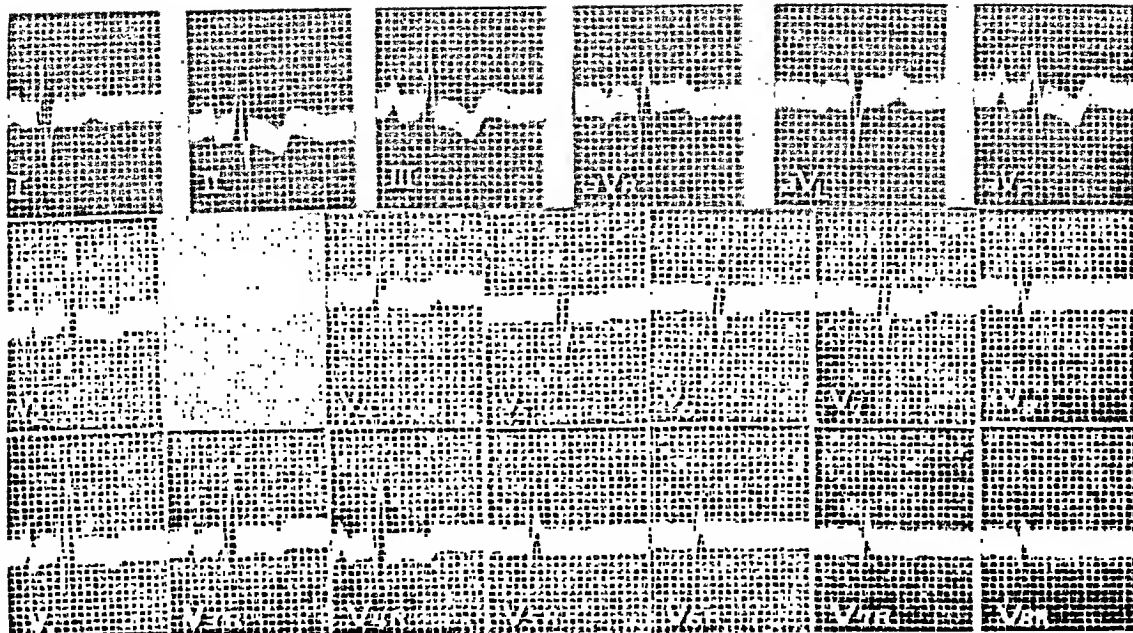


Fig. 17.—Patient J. R., arteriosclerotic and pulmonary heart disease with intraventricular block. In the standard, extremity, and precordial leads, symbols have the same meaning as in previous records. The precordial leads were recorded at 0.5 N sensitivity of the string. The QRS interval in the standard leads was 0.094 second. Time lines, 0.04 second.

To be noted are the R wave and splintered R' in Leads V_1 and V_2 ; the absence of splintering of R' in Lead V_{3R} and other leads farther to the right; the transitional nature of the ventricular complexes in Leads V_3 and V_4 ; and the small Q (barely perceptible, see Fig. 19) in Leads V_5 to V_6 .

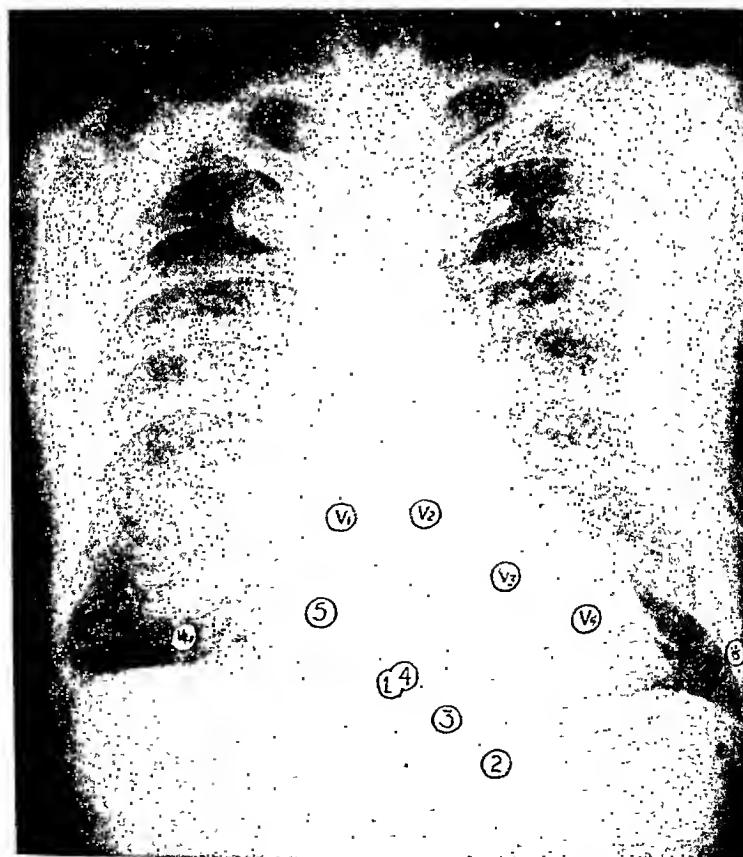


Fig. 18.—Patient J. R. Teleroentgenogram made with patient standing just after cardiac catheterization. Location of the points from which precordial leads were made are indicated by the usual symbols. Location of Lead V_{5R} can be seen at the extreme lower left. Arabic numerals in a circle indicate the location of the intracardiac electrode projected by the central ray of the fluoroscope onto the thoracic surface. At Point 5, the electrode was in the right atrium; at the other points (1 to 4), it was in the right ventricle.

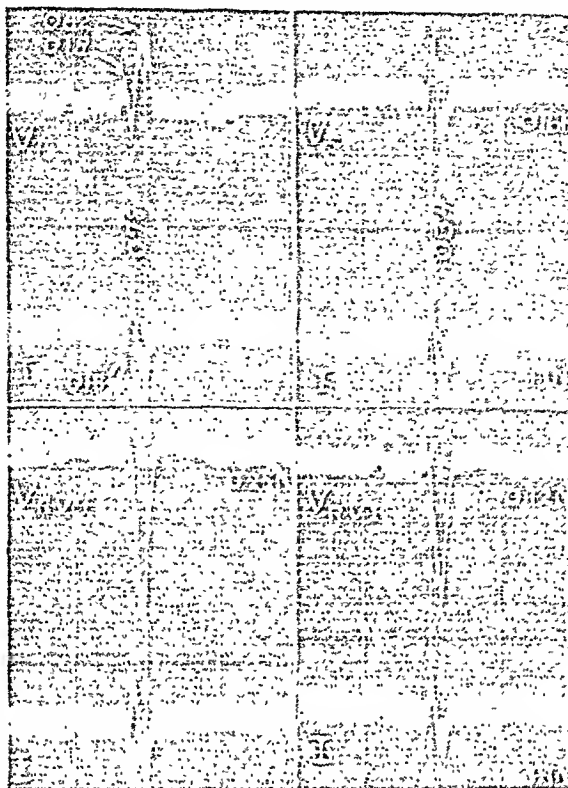


Fig. 19.—Patient J. R. On the left are Leads V_1 and V_{rv4} (right ventricular cavity at Point 4, Fig. 17), each recorded simultaneously with standard Lead I. The two sets of curves have been selected so that the time line marked vertically as 0.078 second (from beginning of QRS in Lead I) is approximately simultaneous in both. To be noted is the simultaneity of R'' in Lead V_1 with the last part of S in Lead I, and with the ascending limb of the S wave in the cavity lead. The R wave in Leads V_1 and V_{rv4} , and the Q wave in Lead I, are simultaneous. R' in Lead V_1 is simultaneous with the first part of S_1 and with the peak of S in the cavity lead.

On the right are Leads V_5 and V_{rv1} (right ventricular cavity at Point 1, Fig. 17), each recorded simultaneously with Lead I. The two sets of curves were selected so that the timeline marked vertically as 0.034 second (from beginning of QRS in Lead I) is approximately simultaneous in both. This demonstrates the simultaneity of R waves in Leads V_5 and I with the notch on the descending limb of the S wave in the cavity lead. String sensitivities were as noted. Time lines, 0.2 second.

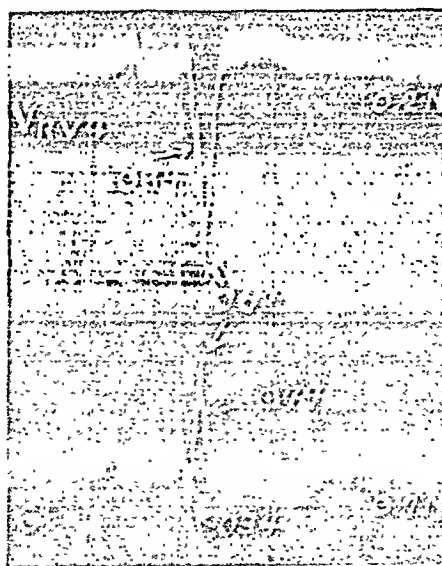


Fig. 20.—Patient J. R. A lead from the right ventricular cavity (V_{rv4}) was recorded simultaneously with a precordial lead; the exploring electrode of the latter was placed on the chest directly over the intracardiac lead, and the indifferent electrode on the left leg (CF). Figures indicate time of deflections with respect to the beginning of QRS in Lead I. Absence of positivity in the cavity, except initially, is noteworthy. Sensitivities of the strings were as noted. Time lines, 0.2 second.

The R wave in the lead from the ventricular cavity was simultaneous with the small R wave in Leads V_1 and V_2 , and with the Q wave in Leads I, V_5 , V_6 , and V_7 . The notch on the descending limb of the S wave of the intracardiac lead was simultaneous with the S in Leads V_1 and V_2 , and with the R in Leads I, V_5 , V_6 , and V_7 . R' in Leads V_1 and V_2 was simultaneous with the peak of S in the cavity lead, but the second notch of R (R'') in Leads V_1 and V_2 occurred at a time when negativity of the right ventricular cavity was rapidly diminishing. Written simultaneously with R'' was the last peak of the S wave in Leads I, V_5 , V_6 , and V_7 . These relationships are fairly easily seen in the curves of Fig. 19, where an attempt was made to align on the left the simultaneous events occurring with R'' of Lead V_1 , and on the right the events occurring simultaneously with R in Lead V_5 .

The origin of some of these relationships is quite clear; of others, quite obscure. It seems certain that the small R wave in leads from the right side of the sternum and from the right ventricular cavity, and the Q wave in leads from the far left side, as well as the Q wave in Lead I, resulted from early excitation of the left side of the interventricular septum. The simultaneity of the ascending limb of R in leads from the left and the initial part of the descending limb of S in the right ventricular lead strongly suggests that the latter event in the cavity was principally due to propagation of the impulse through the lateral wall of the left ventricle. Although this explanation is difficult to sustain on the basis of the laws governing currents in volume conductors, further credence is given to it by the fact that the peak of the R wave in Lead V_5 was simultaneous with the notch located approximately halfway down on the descending limb of the S wave found in the cavity lead (Fig. 19).

The peak of R' in Lead V_1 was simultaneous with the peak of S in the lead from the cavity, which supports the belief that the electromotive force responsible for these deflections was the same, and that this force probably was acting across the wall of the right ventricle. Disturbing, of course, is the fact that this did not occur in other cases (W. F. and A. K.) with right ventricular hypertrophy. Further, and contrary to the theories thus far developed, is the fact that a longer time was required for the excitation to reach the epicardial surface of the right ventricle than of the left. This was calculated as follows: In Lead V_5 (Fig. 19) the time was measured from the peak of Q (beginning excitation of endocardium nearest the exploring electrode) to the initial peak of S (taken as representing complete excitation of the underlying wall); in Lead V_1 a similar interval was measured from the peak of S (Fig. 17) to the small depression between R' and R'' . It is evident that failure of the last deflection to reach the baseline because of the ascent of R'' introduces an error in the direction of foreshortening. Nevertheless, the figure obtained from the left was 0.034 second and from the right 0.034 second, plus the error referred to. This would mean that the right ventricle was thicker than the left if the variables introduced by indirect leading are disregarded. This, as noted previously, is contrary to anatomic observations, and in this patient the left ventricle was enlarged as well as the right, making a conclusion that the right was thicker than the left even less likely. It is almost

certain that this deflection (peak of S to peak of R' in Lead V₁) was caused by a delay in propagation of the impulse across the right ventricular wall. The exact mechanism involved is unknown, but the block was very probably distal to the right bundle branch. This statement is made because the cavity of the right ventricle was negative except in the early part of ventricular excitation. If the bundle branch was blocked and the septum was excited from left to right, one would expect the right ventricular cavity to be distinctly positive during some period of ventricular excitation^{26,28,29} other than the initial period when positivity normally occurs.²⁴

The R'' in Lead V₁ is interesting in that it occurred at a time when the negativity of the right ventricular cavity was decreasing rapidly (Figs. 19 and 20). It occurred very late in the QRS interval (0.074 second from the beginning of QRS in Lead I). The force responsible for R was of sufficient magnitude, however, to keep the left side of the precordium negative (last peak of S wave in Lead V₅). Therefore, it is not believed to have been caused by excitation of the pulmonary conus alone (as seen in dogs). There would seem to have been some considerable amount of muscle, probably around the entire base of the right ventricle, which was still being excited long after the action current had been extinguished across the remainder of the right ventricular wall. Reasons for saying this are that the base of a hypertrophied right ventricle, unlike the apex, is often thick and solid instead of trabecular. Further, in the present case, a set of precordial leads made one intercostal space below the conventional levels failed to display the R'', and in Lead V₂, made in the fifth intercostal space, it was actually replaced by a small S. This means that the force it represented was proceeding not only to the right but also upward.

SUMMARY

1. The physiologic and anatomic reasons for deviation of the electrical axis to the right are reviewed.
2. In certain patients with myocardial infarction, right axis deviation results when the infarct is so oriented that the left arm is in effect a semidirect lead from the cavity of the left ventricle, and is more negative during ventricular excitation than the right arm.
3. Considerations and data are presented which make it doubtful that the hypertrophied right ventricle, except in rare instances, can cause right axis deviation by itself. Rather, it appears to have its dominant effect on the electrocardiogram by changing the position of the heart in the thorax.
4. In certain diseases characterized by a large right ventricle and conditions in the thorax which favor rotation of the heart about its long axis, it is believed that extreme rotation of this organ with almost complete reversal of the electrical fields of the two ventricles in the thorax may occur.
5. When excitation of all the ventricular muscle requires less than 0.1 second, and right axis deviation is accompanied by a late R' in leads from the right side of the precordium, the deviation and the deflection are probably caused

by a delay in propagation of excitation across the free wall of the right ventricle, this delay being distal to the bundle branch. Under such circumstances the R' may be somewhat exaggerated in size and duration by late components contributed by the base of the right ventricle, particularly if it is hypertrophied.

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FLUOROCARDIOGRAPHY (ELECTROKYMOGRAPHY)*

I. TECHNICAL ASPECTS

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THE importance of obtaining accurate records of the pulsatory changes of the cardiac chambers and the large blood vessels is self-evident. Indirect recording, using sphygmography, phlebography, esophagocardiography, and cardiography, has been employed for this purpose, but all these methods have definite limitations and contain sources of error.

The roentgen ray permits direct visualization of cardiovascular silhouettes and yields more accurate records; tracings of the motion of the cardiac silhouette are well known as roentgenkymograms. The basic principle of roentgenkymography is as follows: A slit in a lead screen is placed in front of and perpendicular to the contour whose pulsation is to be recorded. A film moves in a direction perpendicular to that of the slit. The motion of that point of the contour on which the slit has been centered is recorded by the x-ray beam incident on the film passing across the slit.

Goett and Rosenthal¹ used a single slit, while Hitzenberger and Reich² and Zdansky and Ellinger³ used two slits. Stumpf⁴ constructed a screen containing several horizontal slits a distance of 12 mm. from each other so that kymographic records of the entire cardiovascular silhouette were obtained. Cignolini⁵ invented another multiple-slit apparatus where several slits could be adjusted over points of greatest interest on the cardiac silhouette.

Roentgenkymography was received with great hope, but its limitations were soon recognized. These are of two kinds: those due to anatomic and physiologic conditions and those inherent in the technique applied. The anatomic and physiologic limitations are: (1) Linear movement can be registered graphically in its true excursion only if it is observed perpendicularly to the direction of its progression. If observed at any other than a right angle, the excursion will appear to be smaller than it really is. (2) Only the pulsation of the visible con-

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*Various names may be found in the literature for tracings obtained by means of the fluoroscope and the photoelectric cell.⁸⁻¹³ The best known designation for the method is the name suggested by Henny and Boone,¹⁰ "electrokymography." We have felt that the name should designate the main field of application (cardiology) without omitting the roentgenologic aspect of the method. We have, therefore, proposed¹⁴ the term "fluorocardiography."

tours may be registered, so that no conclusion as to the total change in volume of a chamber may be drawn. (3) Pulsations and changes in volume of the cardiac chambers and large vessels are transmitted to adjacent structures; this is particularly true of the transmission of ventricular pulsations to the auricles. The pulsations observed at the surface of these structures often represent a summation of their own weak pulsation plus all transmitted pulsations. (4) The heart performs several types of movements, such as rotation, lateral shift, and elevation of its apex. Also, the effect of respiration on heart motion must be taken into account. These movements distort those solely due to changes in volume of the chambers. These considerations make it clear that the amplitude and even the direction of individual pulsations may be subject to complicated distortions and that any evaluation of the tracings must take into consideration all of these sources of interference.

The limitations in the use of roentgenkymography consequent to technical factors are (1) the difficulty of applying the apparatus in a position perpendicular to the contour to be plotted because of the rigidity of the slits; (2) the short duration of the records obtained (only three or four cycles in Stumpf's multiple-slit kymograph); (3) insufficient speed of the tracings; and (4) inability to simultaneously record on the same film other tracings of the cardiac action (electrocardiogram, heart sounds, pulse waves, and so forth). Attempts have been made^{5,6} to overcome these weaknesses by faster recording over a longer period of time, or by densometric transcription of the original records,⁴ but no great improvement resulted.

Various attempts have been made in the last fifteen years to record fluoroscopic phenomena by means of phototubes. The first of these, by Hjelmare⁸ in 1932, was unsuccessful, while the second attempt, by Heckmann⁹ in 1937 (actinography), was also soon abandoned.

In 1945, Henny and Boone¹⁰ made a significant advance when they used a multiplier phototube with a slit connected with the electrocardiograph; a simultaneous carotid pulse tracing was used for the timing of the waves. The apparatus was called an electrokymograph. An improved version of this apparatus has been described recently by Henny, Boone, and Chamberlain,¹¹ who reported on clinical studies in progress.

Other roentgenkymographic devices which operated on the photoelectric principle were described in 1946. Lian and Minot,¹² used a phototube connected with a galvanometer for the study of cardiovascular phenomena; they called their method radioelectrokymography and used the electrocardiogram as a timer. Marchal¹³ used a very sensitive apparatus for the study of pulmonary vascular phenomena; he called his method kinedensigraphy.

THE APPARATUS

The transducer employed in this investigation is fundamentally the Henny, Boone, and Chamberlain electrokymograph, plus modifications made in order to increase the sensitivity or magnitude of amplification. However, increased sensitivity proportionately increased the amount of artefact, and complete freedom

from artefact is imperative for accurate study of slight motions and variations in density, especially in the oblique positions. The modifications that were finally introduced primarily deal with increasing the ratio between artefact level and degree of amplification (Fig. 1).

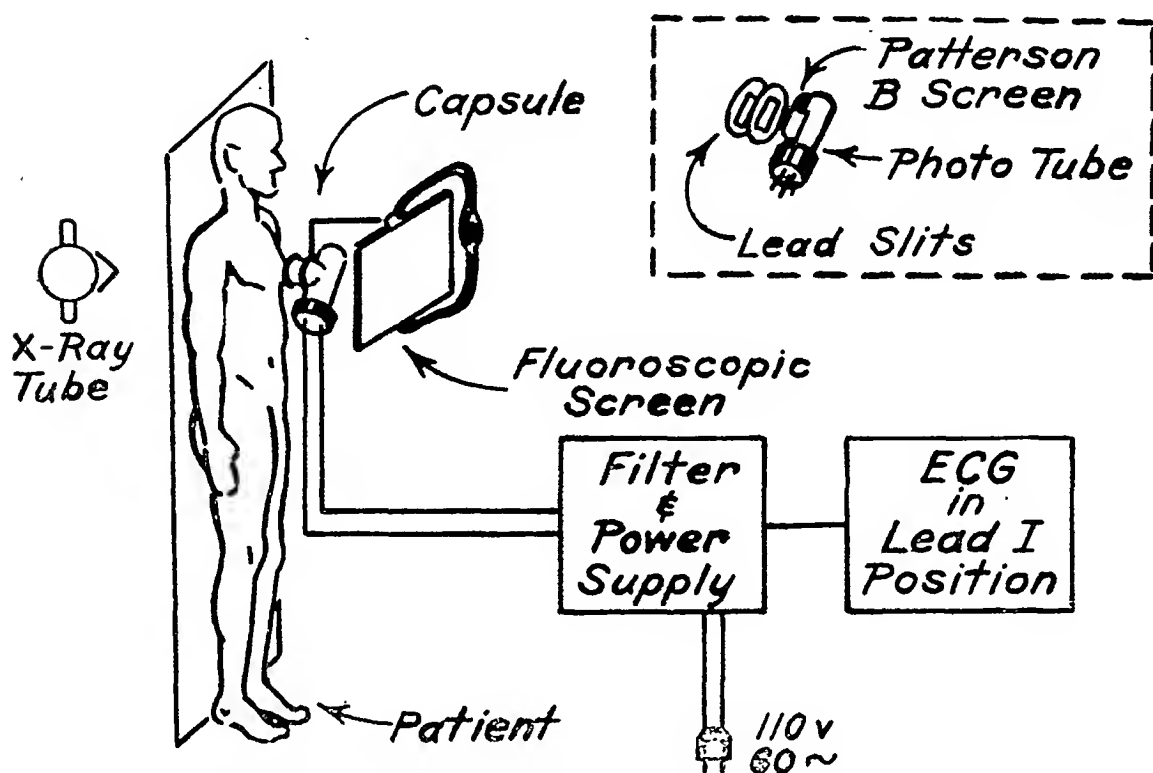


Fig. 1.—Schematic diagram of the arrangement for taking fluorocardiograms.

The transducer was coupled to either a Sanborn Stethocardiette or a Tri-Beam Stethocardiette. The Stethocardiette was used for simultaneous phonocardiogram and fluorocardiogram registration. The Tri-Beam apparatus was used when an additional pulse tracing or fluorocardiogram was desired.

The apparatus is so arranged that when the long axis of the slit is placed in the direction of motion of the portion of the silhouette being studied, a contractile motion registers as a downward or negative wave. If the slit is placed completely within the silhouette area, *densograms* are registered; an increase in density registers as an upward or positive wave and a decrease in density as a downward wave.

As in the Henny, Boone, and Chamberlain electrokymograph, the main part of the apparatus is an electron multiplier phototube.* This is a high vacuum bulb similar in physical appearance to the conventional radio tube. Internally, it consists of a light-sensitive photocathode, a system of nine secondary emission electrodes called dynodes, and a collector anode. The phototube has a maximal response to light, with a wave length of 4,200 Angstroms which is in the blue region.

*This tube is produced by the Radio Corporation of America, Camden, N. J., and is designated 931-A.

The sensitivity of the phototube is 8,200 microamperes per microwatt and the maximum luminous sensitivity is 10 amperes per lumen. The electron multiplier is capable of a maximum current amplification of approximately one million times. The sensitivity of the photocathode to green radiation (approximately 5,000 Angstroms) is about 70 per cent of the maximum response in the blue portion of the light spectrum.

When the photocathode is exposed to light, a proportionate number of electrons are released and immediately attracted to a dynode which is at a positive potential with respect to the photocathode. The surface of the dynode is treated for secondary emission so that each electron which originates at the photocathode displaces several additional electrons at the first dynode. These secondary electrons are then directed to a second dynode which is at a potential more positive than the first dynode surface and they, in turn, displace many more electrons. Since this multiplication process is cumulative in the nine stages of amplification, the maximum overall current amplification attainable is approximately one million times.

As was done by Henny, Boone, and Chamberlain with different types of screens, a strip of Patterson B screen is cemented to the glass envelope of the electron multiplier phototube directly in front of the photocathode. When the x-rays strike the fluorescent screen, the light emitted by the screen is picked up by the photocathode and transformed into equivalent photoelectrons and amplified by electron multiplication. Thus, the electrical output of the 931-A tube varies in proportion to the movement of the silhouette within the opening of the slit. The output of the tube is, in turn, fed into the electrocardiographic channel through a potentiometer which functions as a sensitivity control.

Densograms of the silhouette are registered in a similar manner. The strip of Patterson B screen gives off more or less light to the photocathode as the transparency of the silhouette varies.

As has been observed by Henny, Boone, and Chamberlain, the question of interference elimination is obviously of utmost importance. There are three forms of interference which must be eliminated, namely: (a) electrostatic radiation from the high tension x-ray equipment; (b) flicker due to the cyclic discontinuity of the x-ray emanations; and (c) fluctuations of the power line.

The elimination of interference caused by the high tension x-ray equipment was the least difficult in that only complete electrostatic shielding of the electrokymographic circuit was necessary. A well-shielded electrocardiograph apparatus will not pick up this electrostatic radiation, provided the input circuit is completely shielded. Similarly, the piezoelectric type sphygmographic attachment,^{17,19} which may be used simultaneously on the three channel recorder, is a completely shielded component which is the input to an electrocardiographic channel. The phonocardiographic channel, which is systematically used by us, is likewise shielded and completely free of electrostatic interference. Modern roentgenoscopes are sufficiently noise-free as to produce negligible artefact in the phonocardiograms.

The anode potential supplied to the x-ray tube may be obtained by full-wave or half-wave rectification. A full-wave rectifier applies to the anode of the

x-ray tube pulses which are twice as frequent as those of the power line. That is, if the frequency of the power line is 60 cycles per second, the output of the full-wave rectifier is 120 pulses per second. A half-wave rectifier, on the other hand, supplies 60 pulses per second to the anode of the x-ray tube if the power line is of the 60 cycle per second variety. Thus, the fluorescent screen flickers either 120 or 60 times per second, depending upon whether full- or half-wave rectification is used.

For ordinary roentgenoscopic application, the flicker is of no consequence because the human eye cannot perceive it. However, in this transducer the flicker is transformed into a cyclic interference in the tracing. The magnitude of flicker is so much greater than that of the waves of the tracing that the latter are completely masked.

Henny, Boone, and Chamberlain, in order to suppress the flicker interference, employed a tuned filter. The characteristics of the filter they used permitted a maximum attenuation of the flicker interference approximately one thousand times. When the transducer with increased amplification was used, we found that one thousandfold attenuation was inadequate with the degree of amplification we used. As a result, to make possible the registration of slight silhouette movements or density variations imperceptible to the eye, a two-stage resistance-capacitance type parallel-T network attenuator was found necessary. The essential differences between the filter used by Henny, Boone, and Chamberlain and the one used in our models are: (a) Our filter attenuates the 60 or 120 cycle per second interference at least *one hundred thousand times*, as compared with an attenuation of *one thousand times* in the Henny, Boone, and Chamberlain model. (b) The configuration and spectral width of the filter used in our tests affects the overall response speed to a lesser degree than does the Henny, Boone, and Chamberlain model for equal magnitudes of attenuation.

The significance of (a) is obvious and needs no further discussion. The technical analysis of item (b) is rather complex; however, the significance may be illustrated as follows: If the galvanometer which is used in conjunction with the transducer has a deflection speed of 0.01 second, we observed that the effective speed due to the tailing off of the filter envelope when the filter was tuned to 120 cycles per second was approximately 0.02 second. If the filter is tuned to 60 cycles per second, the effective galvanometric speed is reduced by a greater amount. Our tests showed that the "tailing off" effect present in the Henny, Boone, and Chamberlain filter modified the speed more than did ours. This phenomenon is an extremely important consideration, especially when fluoroscopes with half-wave rectification are used. It should be stated here that a thorough investigation must be made to determine what the minimum effective speed must be so that the tracing will not be distorted. Of course, the introduction of equalizer circuits may minimize or completely eliminate any possible distortion. Also, filter systems which are more free of the "tailing off" effect may become available.

If electrocardiograms are to be taken simultaneously with the fluorocardiograms, similar attenuators must be interposed between the subject and the electrocardiographic apparatus. Otherwise, the unshielded patient will pick up

sufficient electrostatic radiations from the high tension components of the x-ray equipment to completely mar the electrocardiogram.

The graduated potentials that are applied to the nine dynodes of the electron multiplier phototube are obtained from the alternating current power line. That is, the power line potential is transformed to the appropriate voltage, then rectified, filtered, and divided among the electron multiplier elements. Due to the extremely low frequency amplification that the apparatus must employ in order to register the minute changes in the silhouette, the potentials that are applied to the phototube elements must be well regulated. Commercial power lines are known to have instantaneous voltage fluctuations to the extent of several volts. These fluctuations must be regulated or smoothed out before application to the phototube elements or they will register graphically in superposition upon the waves of the tracing. Since these fluctuations are several thousand times as large as the potential variations emitted by the photocathode when registering slight silhouette changes, they would completely mar the record.

Henny, Boone, and Chamberlain regulate the line voltage fluctuations by means of a voltage regulating transformer which is interposed between the electrokymograph and the commercial power line. These stabilizing transformers are in common use in electrical equipment and are commercially available from transformer manufacturers. The common variety of regulating transformer is rated to maintain the output voltage within plus or minus 1 per cent for a total primary variation of 30 per cent. Specially adjusted regulating transformers may be obtained in which the regulation is improved to approximately 0.5 per cent. We observed that the degree of regulation obtainable with a regulating transformer was insufficient to eliminate all the effects of line voltage fluctuation when the sensitivity of the transducer was increased. The line voltage fluctuations were regulated in our experimental models to a point at which the maximum fluctuations, whether instantaneous or gradual, produced insignificant artefact in the tracing. This was accomplished by electronic regulation, which is capable of regulating voltage variations much more effectively than is possible with the transformer method. There are several well-known methods for obtaining electronic regulation which are well described in the electronic literature.

Van Allen¹⁶ in his investigation on different types of fluoroscopic screens for their phosphorescence or lag, found that the green fluorescent Patterson type B screen showed the smallest amount of lag. The result of Van Allen's studies demonstrates that the error due to phosphorescent lag is less than 1 per cent in our device.

Increased sensitivity was obtained in our experimental models by optimum impedance matching between the electron multiplier phototube and the registration apparatus. The loading of the electron multiplier in the Henny, Boone, and Chamberlain electrokymograph creates a severe mismatch with resultant loss in amplification, especially when the string galvanometer is employed without a stage of electronic coupling.

Henny, Boone, and Chamberlain have employed the pulsations of the right carotid artery for timing the waves of their electrokymograms, which were registered by means of a mechanical-optical device. Even though the piezoelectric sphygmogram, as described by Miller and White,¹⁷ is free from the errors inherent in the mechanical-optical system, we chose the phonocardiogram for timing the waves of our tracings. The transmission time of the cardiac sounds in the chest is so infinitesimally small as to be unmeasurable with the registration techniques employed for this type of work. Also, Rappaport and Sprague¹⁸ have shown that the first and second heart sounds may be broken down into events which are of considerable aid in timing the phases of cardiac action. Of course, the third heart sound and auricular sound that often are present in the phonocardiogram may also aid in timing these phases. The phonocardiogram, therefore, is capable of timing practically every mechanical event in the cardiac cycle, which is not true of the sphygmogram.

TECHNIQUE OF APPLICATION

The pickup device (Fig. 2) is attached to a standard fluoroscopic screen by means of a brace. It is centered on the screen so that it is fully exposed to the x-ray beam with the fluoroscopic diaphragm narrowed down to a small field. The slit may be placed either across the border of a moving shadow or fully against the center of the latter. In the latter instance, the tracing is a *densogram*.

Healthy individuals and patients were studied both in the recumbent and sitting positions, the procedure being essentially the same in both instances. A revolving stool was used for studies made with the patient in the sitting position. For every positioning of the pickup device, the shutter is opened for orientation and narrowed again as soon as the slit is brought into position.

As a routine, with the patient in posteroanterior position, we start on the left side, first plotting the apex of the heart just above the diaphragm (Fig. 3); another tracing on the upper part of the left ventricle is then taken. This study is followed by that of the appendage of the left auricle, which often is better visualized by a 10° to 15° rotation toward the left oblique position. The pulmonary artery usually is visible, but sometimes it is advantageous to turn the patient toward the right oblique position through an angle of 10 to 15 degrees. Next, the aortic knob, corresponding to the distal portion of the aortic arch, is easily brought into position. The descending aorta can be studied in the left oblique position by placing the slit vertically either against the spine or between it and the heart. We then have a *densogram* of the aorta (Fig. 4).

On the right side we usually trace the right auricle at its most prominent point; occasionally, also at a lower point of its contour. In some cases a good tracing is obtained by using the uppermost portion of the right auricle with some rotation toward the left oblique position; in this case we assume that we are centering upon the appendage of the right auricle.

The ascending aorta can be studied in normal young subjects by using a 10° left oblique position. Its study in the posteroanterior position is possible in mature or old individuals when atherosclerosis and dilatation of the vessels are present.

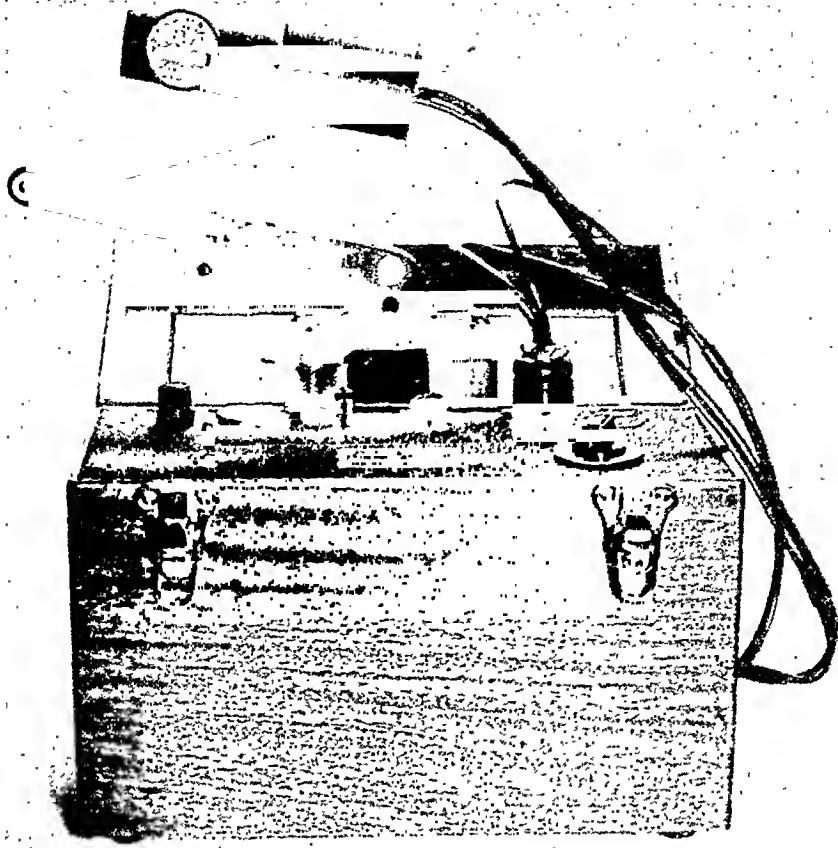


Fig. 2.—The fluorocardiograph. The pantograph and capsule arrangement, which is normally fastened to the screen of the fluoroscope, is here shown above the control panel of the apparatus.

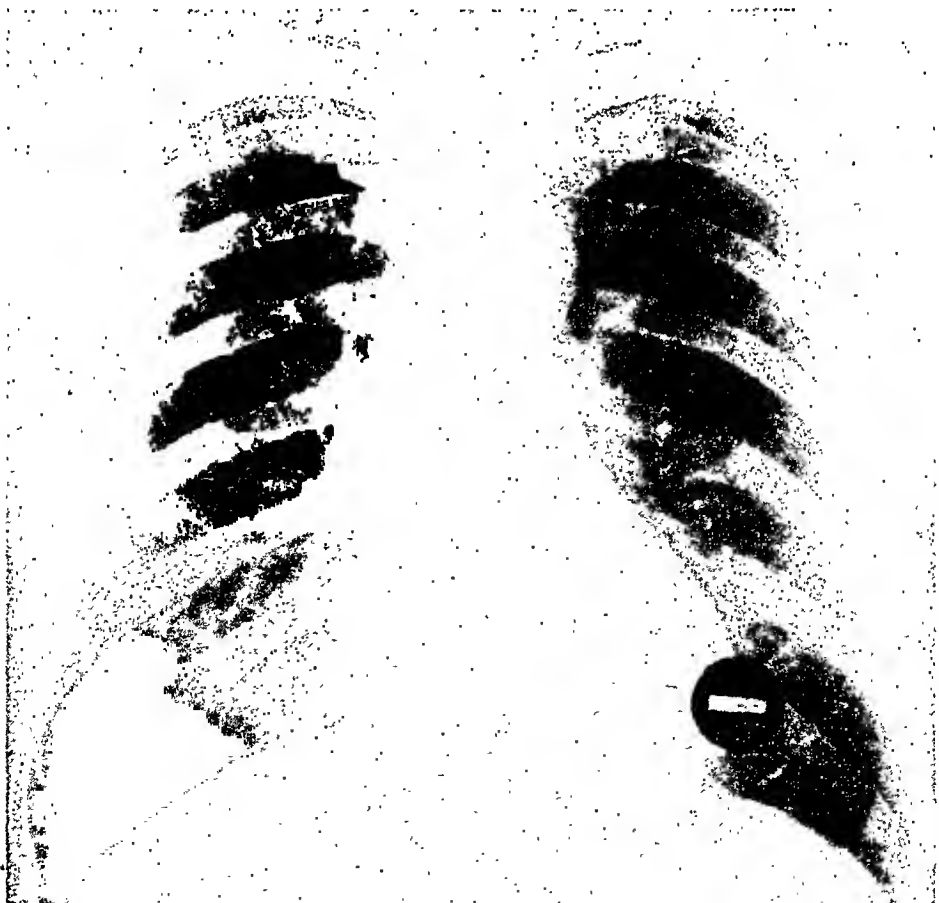


Fig. 3.—Chest film in posteroanterior position. The slit of the schematic pickup device is placed at the cardiac apex.

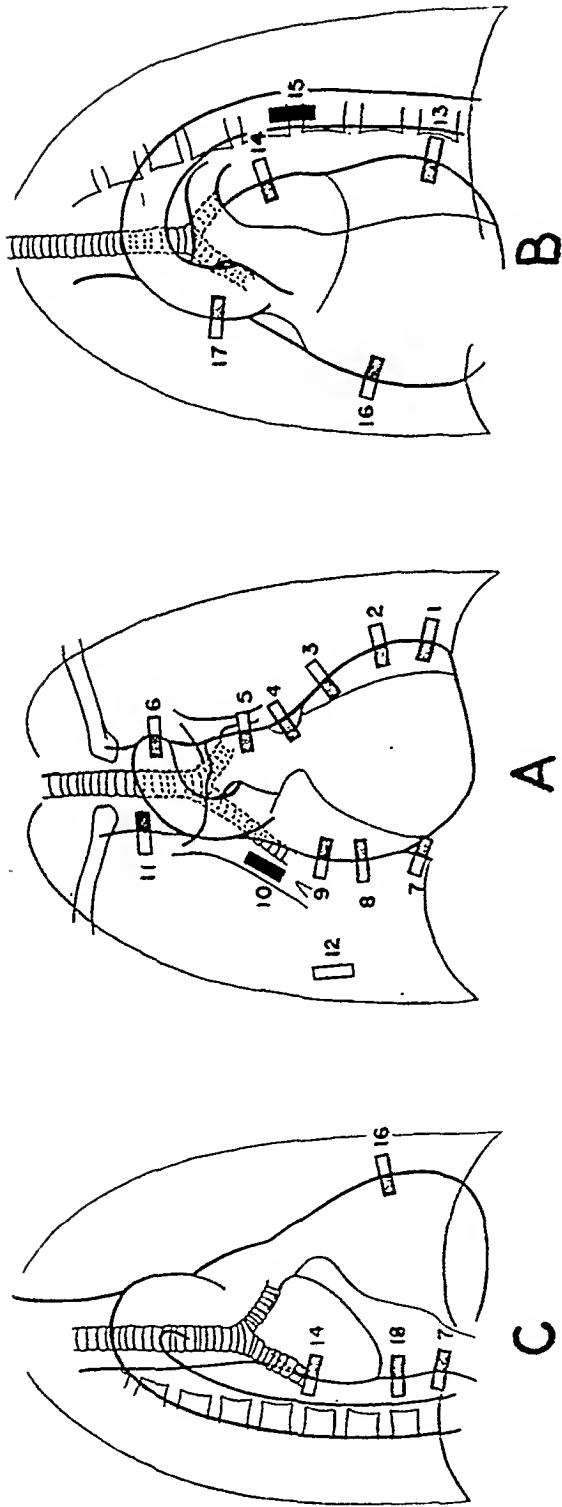


Fig. 4.—Standard positions of the silt for recording the motion of various cardiovascular and pulmonary structures. *A*, Postero-anterior position: (1) apex; (2) left ventricle, half way position; (3) left ventricle, upper portion; (4) left auricular appendage; (5) pulmonary arch; (6) aortic arch; (7) inferior vena cava; (8) right auricle, mid-portion; (9) right auricle, upper portion; (10) right hilar shadow (densogram); (11) superior vena cava; and (12) right lung, lower lobe (densogram).
B, Left anterior oblique position: (13) left ventricle, posterior wall; (14) left auricle, posterior wall; (15) descending aorta (densogram); (16) right ventricle, anterior wall (this is usually plotted in the straight lateral view at the level indicated by the diagram); and (17) ascending aorta.
C, Right anterior oblique position: (7) inferior vena cava; (14) left auricle, posterior wall; (16) right ventricle (see note in left anterior oblique); and (17) right ventricle, posterior wall.

We have not always been successful in obtaining a satisfactory tracing of the superior vena cava. In addition to greater deflections, similar to those of the jugular phlebogram, there are often a large number of additional vibrations. Since we were working with healthy young individuals, it was occasionally difficult to visualize fluoroscopically the vena cava clearly enough to place the pickup unit correctly. On the other hand, we found it easy to obtain excellent tracings of the inferior vena cava which is seen either in the straight postero-anterior or in the right oblique position. The patient holds his breath in deep inspiration for this procedure.

For the plotting of the hilar pulsations, we preferred the right hilar shadow as the one more clearly exposed. With the intention of plotting a densogram of the hilar vascular convolution as a whole, the slit was placed vertically across the hilar vessels as far away from the vascular shadow as possible.

For the recording of the peripheral pulmonary pulsations, the slit was placed vertically, either over the upper or the lower lobe of a lung, a few centimeters above the diaphragm. This tracing is a *densogram* of the lung.

For better exposure of the left auricle we chose a right oblique, sometimes almost a lateral, position, and placed the slit from 3 to 4 cm. below the level of the bifurcation of the trachea across the contour of the auricle where it is well seen against the clear space of the right bronchus. Whenever the left auricle is extremely dilated and its borderline is not clear, a *densogram* of the chamber is recorded. In many cases, however, the left oblique position is sufficient for a good tracing.

The pulsation of the right ventricle is best picked up in the straight lateral view just above the point where it separates from the anterior chest wall. For reasons not entirely explained so far, we have not been always successful in obtaining a satisfactory tracing of the right ventricle with a normal subject in a sitting position, although there has been no difficulty in obtaining a satisfactory one with the subject in the recumbent position. However, patients with right ventricular hypertrophy usually yield good tracings in the sitting position. Actually, the tracing of the right ventricle is often a *densogram* of this chamber.

The roentgen exposure of the skin of the patient during this procedure is within safe limits. Our ordinary routine technique for chest fluoroscopy is used, that is, 5 milliamperes at 65 to 70 kilovolts with an inherent filter of 1 mm. of aluminum. The orienting fluoroscopy with the wide open shutter takes only a few seconds. With the pickup device in place, the shutter is narrowed to an opening of about 25 square centimeters. The actual recording does not require more than two minutes, including the adjustment of the amplifier. Thus, with the portion of the skin changing with each position of the pickup device, the dose applied to the skin is within safe limits.

INTERPRETATION OF THE TRACINGS

The polarity of the apparatus is arranged so that an increase in light causes a downward movement of the tracing. Therefore, any fall in the curve indicates either an inward motion of the cardiac border if the slit is across the border

of the cardiac silhouette, or a decrease in the thickness of the structure if the slit is over a homogenous area, and a densogram is recorded. On the other hand, every rise of the curve indicates either expansion of the cardiac or arterial border or increased thickness of the structure (densogram).

Any kymographic wave occurring before the first large vibration of the first sound, as recorded in the phonocardiogram, is presystolic; any wave occurring after the last vibration of the second sound is diastolic; any wave taking place between the beginning of the first sound and the end of the second is systolic.

The tracing has no well-defined baseline. An arbitrary zero line can be made by drawing a line, passing through that point of the curve which is between the auricular and the ventricular waves of the cardiac tracing (if the rhythm is normal). Its equivalent point, namely, the point from which the ventricular wave begins, can be used if there is no auricular contraction. The foot of the wave will mark the zero point in the tracings taken over the arterial tree of the lung.

We feel that the method is simple, accurate, and satisfactory in the study of cardiac and vascular pulsations.

SUMMARY

Utilizing the Henny-Boone method, but with some modifications, an apparatus has been built which is capable of recording minute pulsations imperceptible to the naked eye. The tracings are obtained by the use of the fluoroscope, an electron multiplier photoelectric cell, a screen with a slit, and a phonocardiograph-electrocardiograph. A technical description of the apparatus and a list of the modifications are given.

As a routine procedure, the phonocardiogram was found preferable as a timer because it is accurate, easy to record, and in close time relation with the valvular events of the heart. The tracings are recorded at a film speed of 75 mm. per second.

The name *fluorocardiography* is suggested for the method, as being more descriptive than previously employed terms.

The pulsations of the following structures have been studied: (a) left and right ventricles; (b) left and right auricles; (c) pulmonary artery; (d) aorta (ascending, arch, and descending); (e) superior and inferior venae cavae; (f) hilar shadows; and (g) pulmonary parenchyma.

The optimum positioning of the slit for obtaining clinically relevant records is discussed. These may be obtained either by placing the slit across the visible border of the visible silhouette or entirely within the shadow of a structure; the latter are *densograms*.

We wish to thank the Sanborn Company of Cambridge, Mass., for their generous help and friendly cooperation. We also wish to thank Doctors W. E. Chamberlain, B. R. Boone and G. C. Henny of the Temple University Medical School for generously putting at our disposal initial unpublished information of a technical character.

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FLUOROCARDIOGRAPHY (ELECTROKYMOGRAPHY)

II. OBSERVATIONS ON NORMAL SUBJECTS

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IN PREVIOUS communications^{1,2} the authors, following the initial work of Henny, Boone, and Chamberlain,^{6,7} have discussed certain of the technical aspects of photoelectric roentgenkymographic tracings which Henny and associates have termed "electrokymograms" but for which we have proposed the term "fluorocardiograms" as being more descriptive. In these reports, the basic Henny, Boone, and Chamberlain electrokymograph and our modifications have been described. In addition, the x-ray technique and the preferable positions for registering the pulsations of the various portions of the cardiac border, the large vessels, and the lungs are discussed. As a routine procedure, we have used the phonocardiogram as a means for timing the component waves. The physiologic observations which follow are based upon a study of twenty normal subjects whose ages ranged from 15 to 70 years.

GENERAL CONSIDERATIONS

As we have already pointed out,^{1,2} roentgenkymographic tracings of any point of the cardiac silhouette may represent the summation of: (a) Motion due to changes in volume of the chamber in systole and diastole; (b) motion due to rotation and total shift of the heart; and (c) traction resulting from motion of other adjacent cardiovascular structures. The possible causes of traction of any structure upon another are many; in particular, one auricle may show the effect of traction by a ventricle or by the large arteries. These distortions of the pulsatory phenomena proper have been established by classical roentgenkymography (Fig. 1).

The visible changes in volume are greatest in the left ventricle, and decrease in the following order: (a) left ventricle, with highest amplitude at the apex; (b) aorta; (c) pulmonary artery; (d) right ventricle; (e) auricles; (f) venae cavae and hilar shadows; and (g) lungs (Figs. 2 and 9).

These movements may be seen by fluoroscopy for the most part, but detailed analysis is possible only by graphic tracings which are accurate as to time and amplitude.

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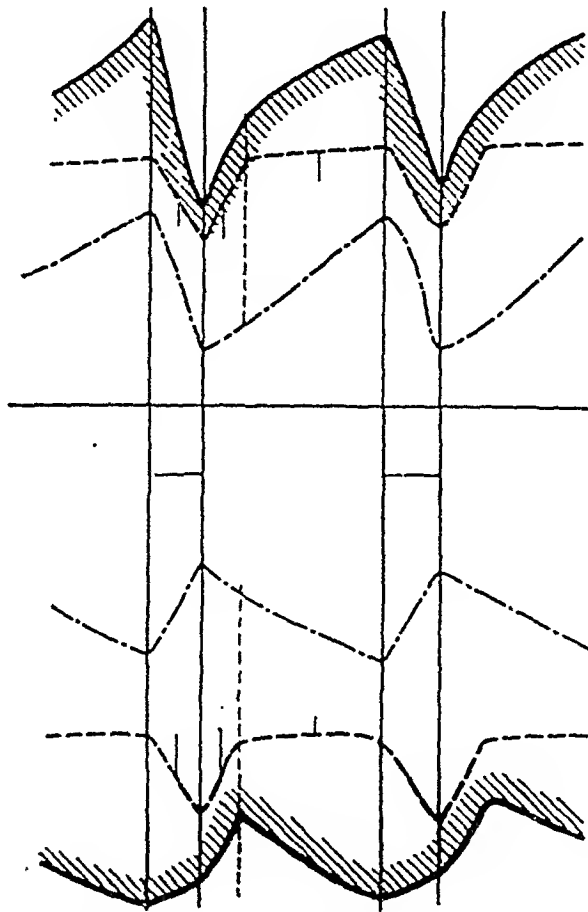


Fig. 1.—Heckmann's scheme of the motion of the left (above) and right (below) heart borders in the roentgenkymogram. The shaded line represents the actual tracing which is the resultant of volumetric changes (dot-dash line) and of positional changes (broken line). (from Roesler, Hugo: Cardiovascular Roentgenology, Springfield, 1945, Charles C. Thomas, Publisher.)

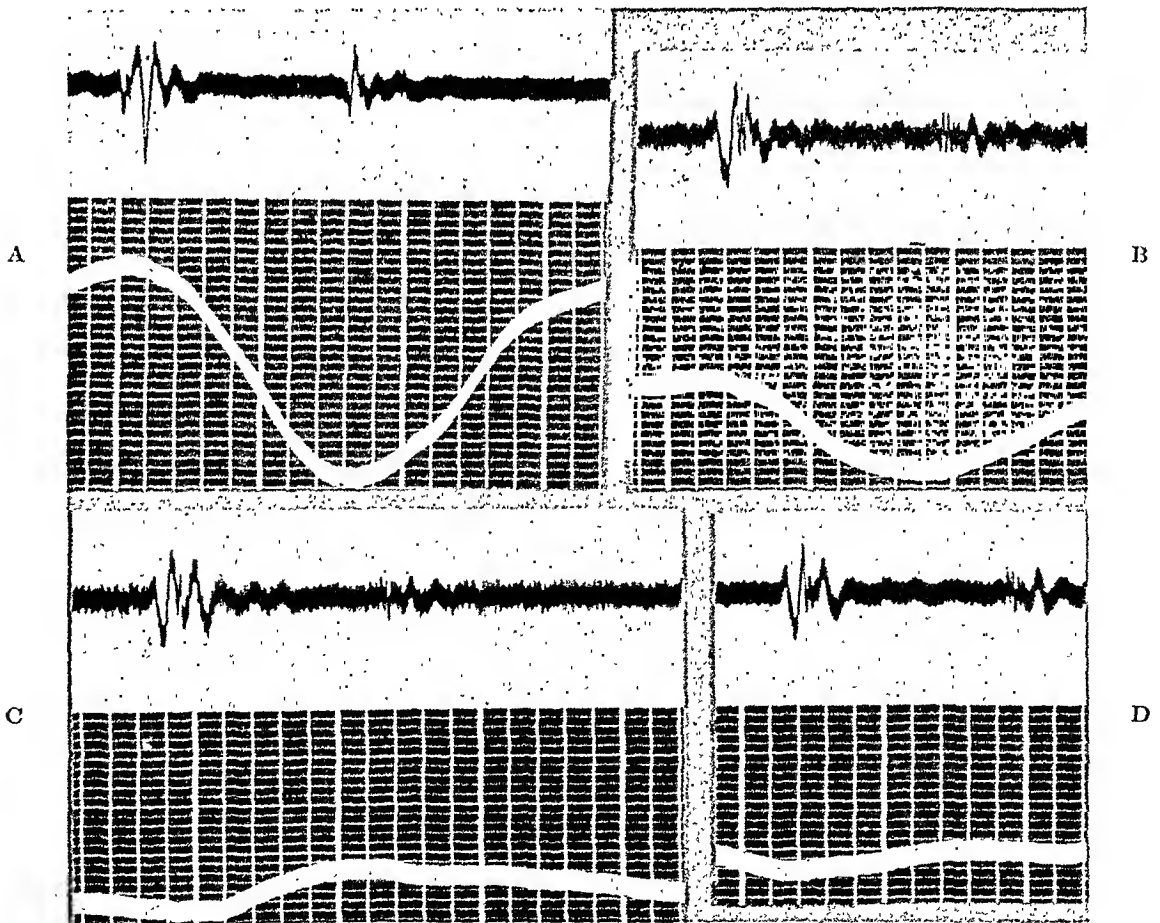


Fig. 2.—Comparison of four tracings recorded on the same individual with the same amplification. A, Apex; B, high left ventricle; C, aortic arch; and D, pulmonic arch. The phonocardiogram in A appears somewhat different in configuration, although taken on the same subject. This is due to relocation of the microphone for optimum visualization of the heart. Similar phonocardiographic differences will occur in the subsequent illustrations for this reason.

SPECIAL ANALYSIS

Left Ventricle (Fig. 3).—

Apex: Slight differences can be found between the fluorocardiograms registered in the supine, and those taken in the sitting position.. In general, a small positive wave can be recorded either immediately before or during the first group of vibrations of the first sound-complex. The most logical interpre-

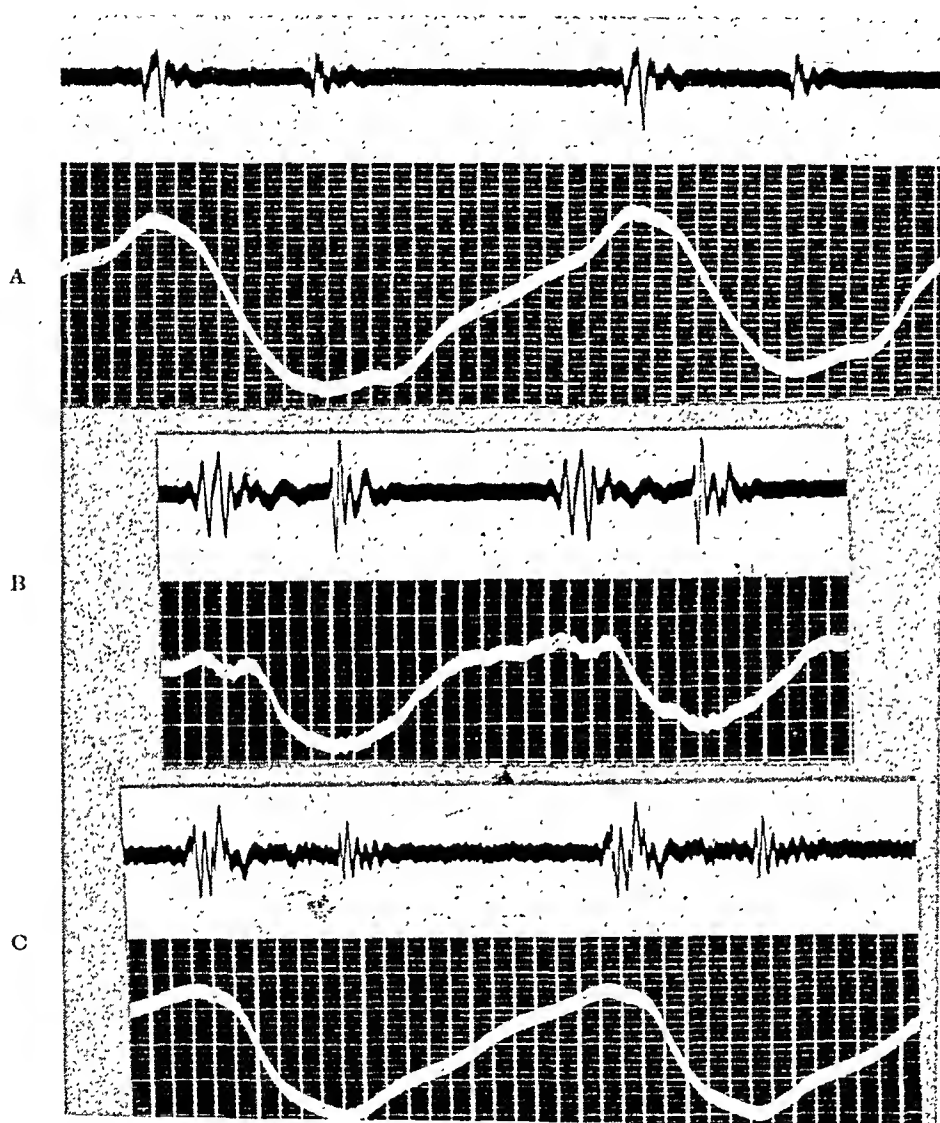


Fig. 3.—Tracings recorded in the sitting position in three different subjects. The distention of the ventricular wall because of auricular contraction is mainly apparent in tracing B. Tracings A and B were recorded at the apex. Tracing C was taken in Position 3.*

tation is that the left auricular contraction pushes a certain amount of blood into the left ventricle, causing a dilatation of its apical region; tracings recorded on patients with auricular fibrillation do not show this small positive wave. The tension period (isometric contraction) of ventricular systole is evidenced by the small depression, probably because of slight torsion of the heart (Fig. 3, B).

*This and other positions which will be referred to have been described in a previous paper.²

In a tracing recorded at the apex, the main ventricular wave consists of a large downward deflection which starts at the end of the first sound-complex if this is short, or at the time of the second largest vibration of the same sound; this has been explained as due to the opening of the aortic valve.⁴ There is, therefore, a striking coincidence between the phases of the fluorocardiogram and those of the phonocardiogram. The beginning of the ventricular wave is due to the decrease in volume of the ventricular mass.

The descending branch of the ventricular wave reaches its lowest point at a time which varies in different subjects and positions. It is apparent that rotation and displacement of the apex, in addition to volume changes, influence the true relationship of the point of maximal fall. In most cases, this point coincides with the largest vibration of the second sound-complex, that is, with the closure of the aortic valve. This precise coincidence, which is more commonly seen with the subject in the sitting rather than in the lying position, proves that the tracing of the volume changes of the left ventricle is accurate in its timing. In some subjects, particularly when they are examined in the supine position, the maximal drop takes place after the completion of two-thirds of ventricular systole and is followed by either a shallow curve or a gently ascending slope. Frequently in the latter cases, a small notch is present at the time of the second sound.

The return of the tracing to the base line does not occur evenly: first, there is a rapid slope which ends at the time of the third heart sound if this sound is present (rapid filling of the left ventricle); this is followed by a more gradual slope, or even a horizontal line, which continues until the beginning of the following cycle. In some cases, a little rebound is present at the beginning of diastole.

Densogram: The densogram of the left portion of the ventricular mass resembles an apical tracing. However, the ascending limb of the curve (diastole) is slower and reproduces less accurately the events of the cardiac cycle.

Convexity of the Left Ventricle: When the slit is placed higher on the convexity of the left ventricular silhouette, the undulations of the tracing reproduce the volume changes of the chamber more faithfully and denote to a lesser degree the extraneous effect of the motion. The total depth of the ventricular wave is approximately 40 to 50 per cent of that recorded at the apex (Fig. 3, A and C). The coincidence between the lowest point of the ventricular wave and the main vibrations of the second sound is seen more regularly in this position.

Other Points on the Ventricular Surface: The left ventricle can be studied in various projections, such as the left anterior oblique (posterior aspect) and the right anterior oblique at 20° or the left posterior oblique (anterolateral aspect). Tracings recorded in these positions give basically the same type of tracing as that of the left margin in the posteroanterior position, except that the waves are smaller and the lowest point of ventricular systole frequently is represented by a shallow curve rather than a sharp angle.

Right Ventricle (Fig. 4).—The study of right ventricular contraction is far more difficult than that of the left. Indirect evidence of right ventricular activity may often be found in the tracings of the right auricle in the postero-anterior view; however, they cannot be considered accurate, even in cases of auricular fibrillation. The best tracings are recorded in the straight lateral view with the slit placed where the cardiac shadow separates from that of the anterior chest wall, or just below this spot. Recording of a slightly higher segment in normal individuals frequently has yielded tracings of an arterial type (pulmonary artery). We feel that the tracings of the right ventricle are a composite of the pulsations of the contour plus a densogram of the anterior part of the right ventricle.

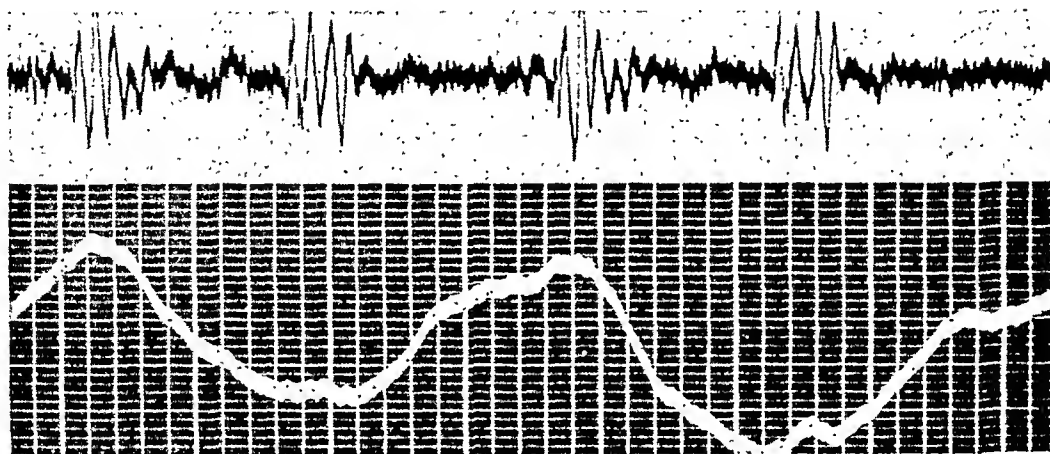


Fig. 4.—Tracing of the right ventricle in Position 16.

The tracing of the right ventricle presents only a small positive wave at the beginning of the first sound-complex. Later, it shows a curve comparable to that of the left ventricle in all details. The absolute amplitude of the right ventricular wave is far less than that of the left. This is not evident in our tracings because higher amplification is displayed except in instances of comparative studies.

Left Auricle (Fig. 5).—Studies of the left auricle were made in three different positions: (a) in a 10° *left oblique* (left auricular appendage); (b) in *left oblique*, at 45 or more degrees; and (c) in *right oblique*, at 45 or more degrees.

While the tracings of the three positions are similar, one of the three is sometimes inferior to the others because of individual conditions.

The typical tracing shows a downward wave which occurs in the presystolic portion of ventricular diastole. This auricular wave is rounded and small in some subjects, but is deep and sharp in others. The beginning of the auricular wave is about 0.14 second before the first sound. However, if the heart rate is rapid, there is no sharp distinction between early diastolic and presystolic waves: only one slow wave is present in diastole with maximum depth at the time of maximum left auricular contraction. The peak of the downward auricular wave is reached either at the time of the first vibration of the first sound-complex or

slightly before. If an auricular sound is present, it is seen during the downward slope of the auricular wave. The presystolic wave is much deeper in patients with left auricular hypertrophy, while it disappears in patients with auricular fibrillation.

After the presystolic wave, the tracing rises sharply at first, then slowly up to the middle of ventricular systole; it often presents two negative waves, one in systole and the other in diastole.

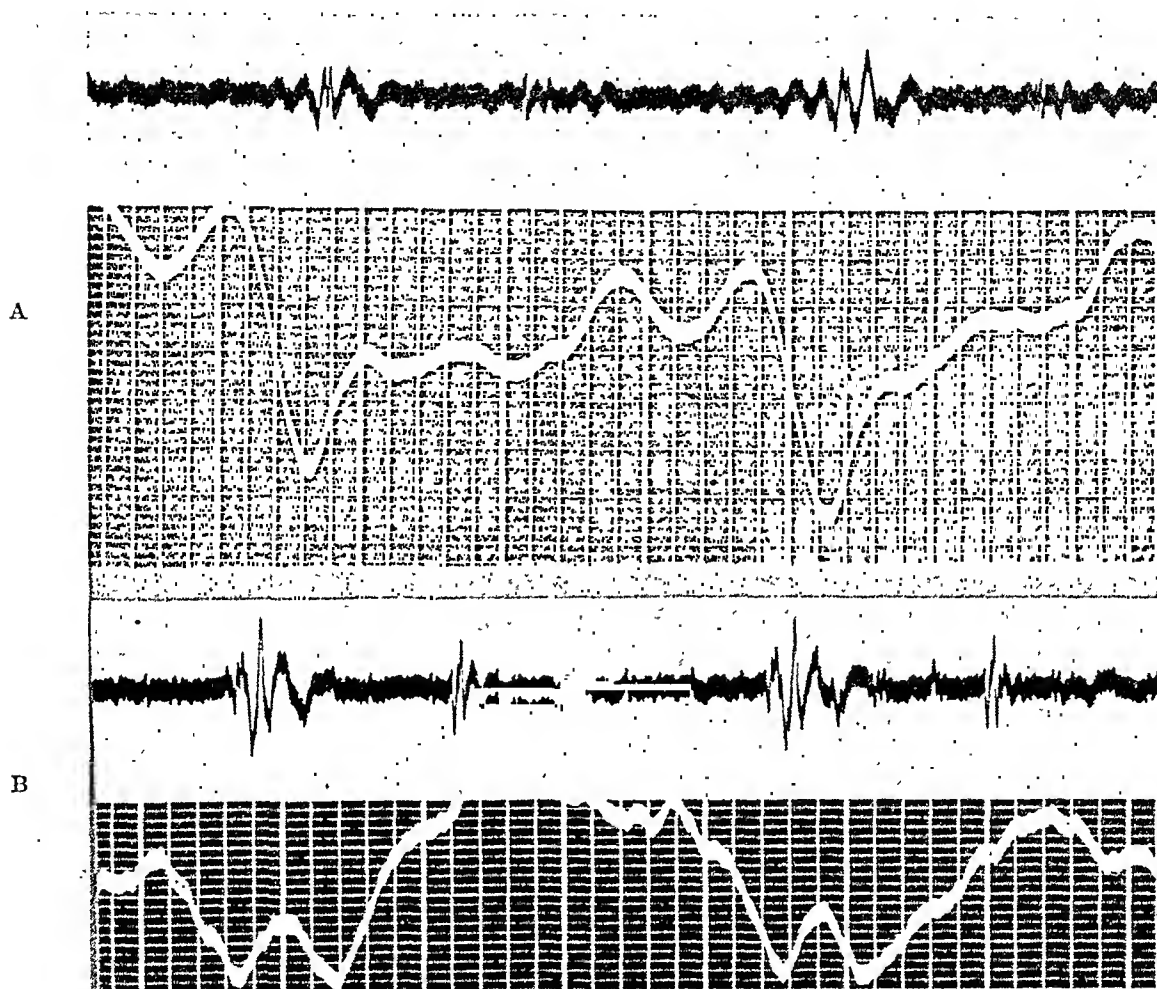


Fig. 5.—Tracings of the left auricle: *A*, Tracing recorded in Position 14 with the subject sitting; *B*, Tracing recorded in Position 4 with the subject lying. Tracing *A* presents a very deep presystolic wave and nearly no trace of ventricular activity. Tracing *B* shows two negative waves, one presystolic, and one in early systole; after the latter, the tracing rises gradually until after the second sound. In both tracings, the auricular wave begins 0.10 second before the first vibration of the first sound-complex while the peak is reached about 0.02 second before it.

The systolic wave of the left auricular tracing is related to the dynamics of the left ventricle. The contraction of the left ventricle lowers the auriculo-ventricular septum; this creates suction within the left auricular cavity which is not immediately compensated for by increased inflow of blood. Therefore, an inward movement of the free auricular wall takes place. This is shorter in duration than the corresponding ventricular contraction owing to the venous inflow which dilates the auricle. The highest level of the tracing is reached not

at the end of ventricular systole, but slightly afterward when the mitral valve opens.

After the end of the systolic wave, a third negative wave may occur, the diastolic collapse. This probably is due to the passive flow of blood into the left ventricle when the mitral valve opens.

When the left auricle is greatly enlarged, but is not visible on the right heart border, and when its dorsal contour is not clearly visible, a densogram can be taken. Such a tracing presents a clear-cut presystolic downward wave. However, this is not as informative as a tracing of the contour, because of interference by the pulsations of the pulmonary veins and branches of the pulmonary artery.

The tracing of the left auricular appendage is sometimes not accurate during ventricular systole if the pulmonary artery is dilated; the record taken in the left oblique position may not be accurate during ventricular systole if the descending aorta is enlarged.

Right Auricle (Fig. 6).—The tracing recorded over the margin of the right auricle is similar to that of the left auricle. Contraction of the auricle during presystole is manifested by a small and rounded downward wave. After

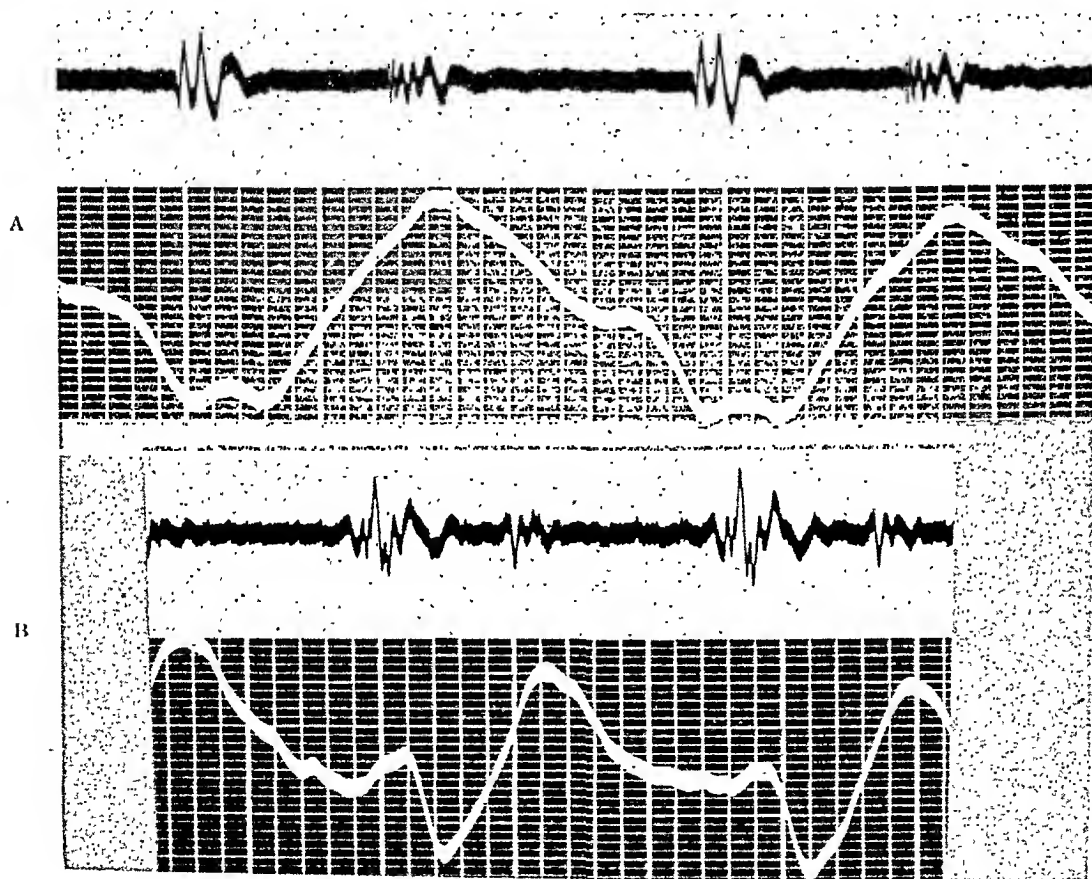


Fig. 6.—Tracings of the right auricle. A, 22-year-old man, in lying position. B, 15-year-old boy, in sitting position. In both cases the slit was placed in Position 8. The auricular wave is small in both cases, but is better visible in A. The ventricular wave is deeper in the sitting position. The maximum rise is reached after the second sound in both cases.

this, the tracing either reaches the base line or rises above it, but drops again during ventricular systole.

Ventricular systole is manifested by a sharp downward wave which often is deeper than the auricular wave. However, it terminates early at about mid-systole. The subsequent course of the auricular tracing varies with the position of the subject. In the sitting position, the tracing rises slowly and attains its maximum height at the time of tricuspid opening; in the recumbent position, the rise is quicker and there may be a convex line which brings the tracing far above the base line. Another drop, however, takes place after the opening of the tricuspid valve, the diastolic collapse.

In summary, there is a presystolic collapse, a systolic collapse, and, frequently, an early diastolic collapse. The early diastolic and the presystolic collapses are apparently due to changes in volume of the auricle, the former because of passive inflow from the right auricle into the right ventricle, and the latter because of right auricular contraction. The cause of the systolic collapse may be open to discussion. We feel that it is due mainly to a decrease in pressure within the auricle because of traction on the auriculoventricular septum, and not to a total displacement. Such a mechanism would give rise to an early end of the systolic wave, because the inflowing blood increases the auricular volume. The same mechanism explains the difference observed in the sitting and supine positions, because there is a greater and faster inflow from the inferior vena cava in the recumbent position.

Whenever there is tachycardia, the early diastolic wave merges with the presystolic wave, indicating that ventricular filling is continuous, first in a passive manner and later as a result of auricular contraction.

While evidence of right auricular contraction is often difficult to obtain by common clinical methods, we have always found a deep, sharp auricular presystolic wave in cardiac patients with sinus rhythm. On the other hand, whenever auricular fibrillation was present, no presystolic wave has been obtained.

Attempts to record a densogram of the right auricle are not always successful due to the superimposition of the right auricular shadow over that of the right ventricle.

Ascending Aorta (Fig. 7, A).—It is not always possible to record a tracing of the ascending aorta in the straight posteroanterior position in normal young individuals because of the fusion of the shadows of different structures. In the left oblique position, a tracing of the ascending aorta is usually possible.

When, however, the ascending aorta is dilated as a consequence of atherosclerosis, hypertension, or vascular syphilis, a tracing can be recorded both in the left oblique position and in the posteroanterior position. In such cases, the tracing is typical and the rise coincides exactly with the second large vibration of the first sound-complex or, if this vibration is not distinct, with the second half of this sound. The tracing of the ascending aorta may assume a plateau-like aspect.

Aortic Arch (Fig. 8).—The tracing of the aortic arch can be obtained in all subjects. It presents marked individual variation in its shape. Its common

features are: (a) a small positive wave during the first part of the first sound-complex, probably due to rising of the aortic valves at the time of isometric contraction; (b) a sharp rise, starting with the second large vibration of the first sound-complex (opening of the semilunar valves) and continuing until the end of the sound; (c) an anacrotic depression in the first part of systole; (d) a peak which usually occurs in the last part of systole but well before the second sound;

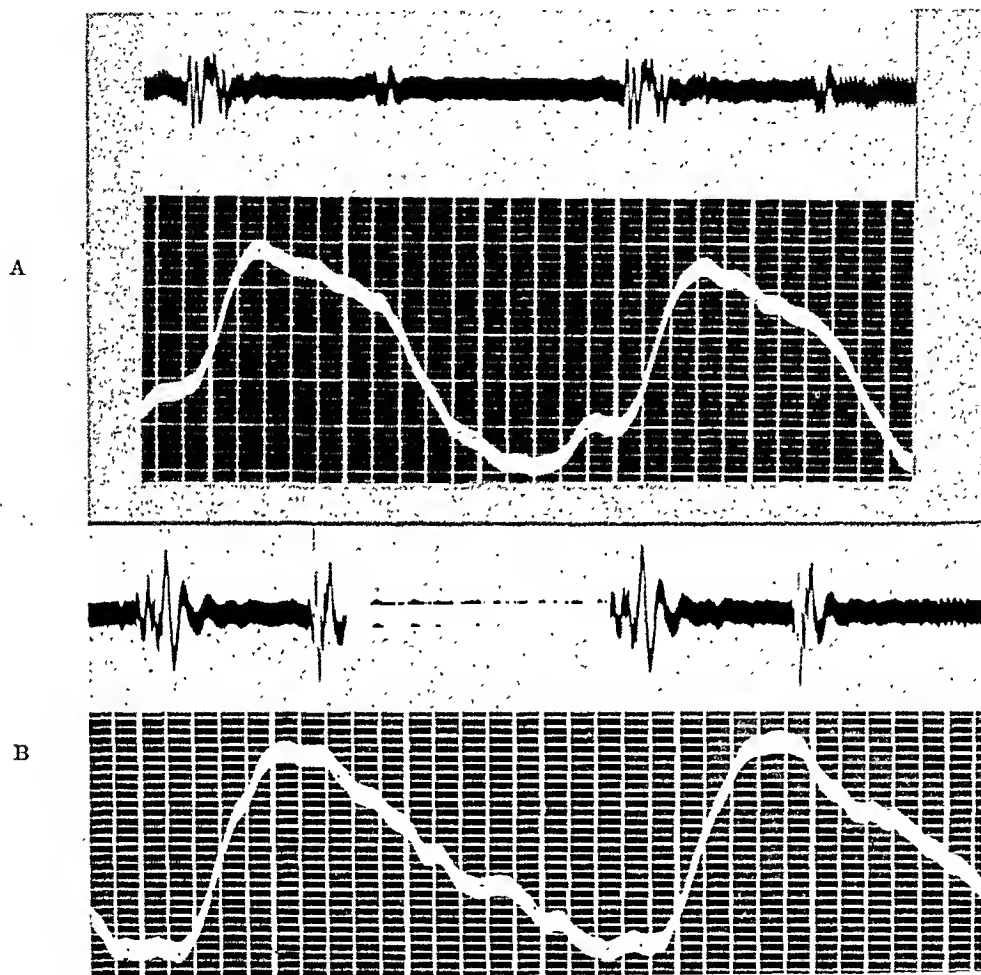


Fig. 7.—Tracings: *A*, of the ascending aorta in Position 17 (70-year-old woman) and *B*, of the descending aorta in Position 15 (25-year-old man). The rise of the pulse takes place at the time of the opening of the semilunar valves in Case *A* and 0.04 to 0.05 second later in Case *B*. The peak of the wave is reached 0.08 second after the opening of the semilunar valves in Case *A* and 0.18 second in tracing *B*.

(e) a predicrotic notch, which may coincide with the second sound or form a short plateau, prolonged slightly after the second sound; (f) a dicrotic wave, which usually is small and rounded; and (g) a few small after-vibrations.

A comparative study of the fluorocardiograms of the aortic and pulmonary arches by simultaneous tracings, as well as by recording each of them simultaneously with the subclavian pulse, has shown a precession of 0.02 to 0.03 second in the rise of the pulmonic pulse over that of the pulse of the aortic arch.

A densogram of the aortic arch gives a tracing which is similar to that just described.

Descending Aorta (Fig. 7, B).—Since the descending aorta often does not present a sharp contour on fluoroscopy, only a densogram is possible in many normal subjects. The tracing is similar to that of the aortic arch, but shows a slight delay in the rise of the pulse in comparison with the rise in the arch.

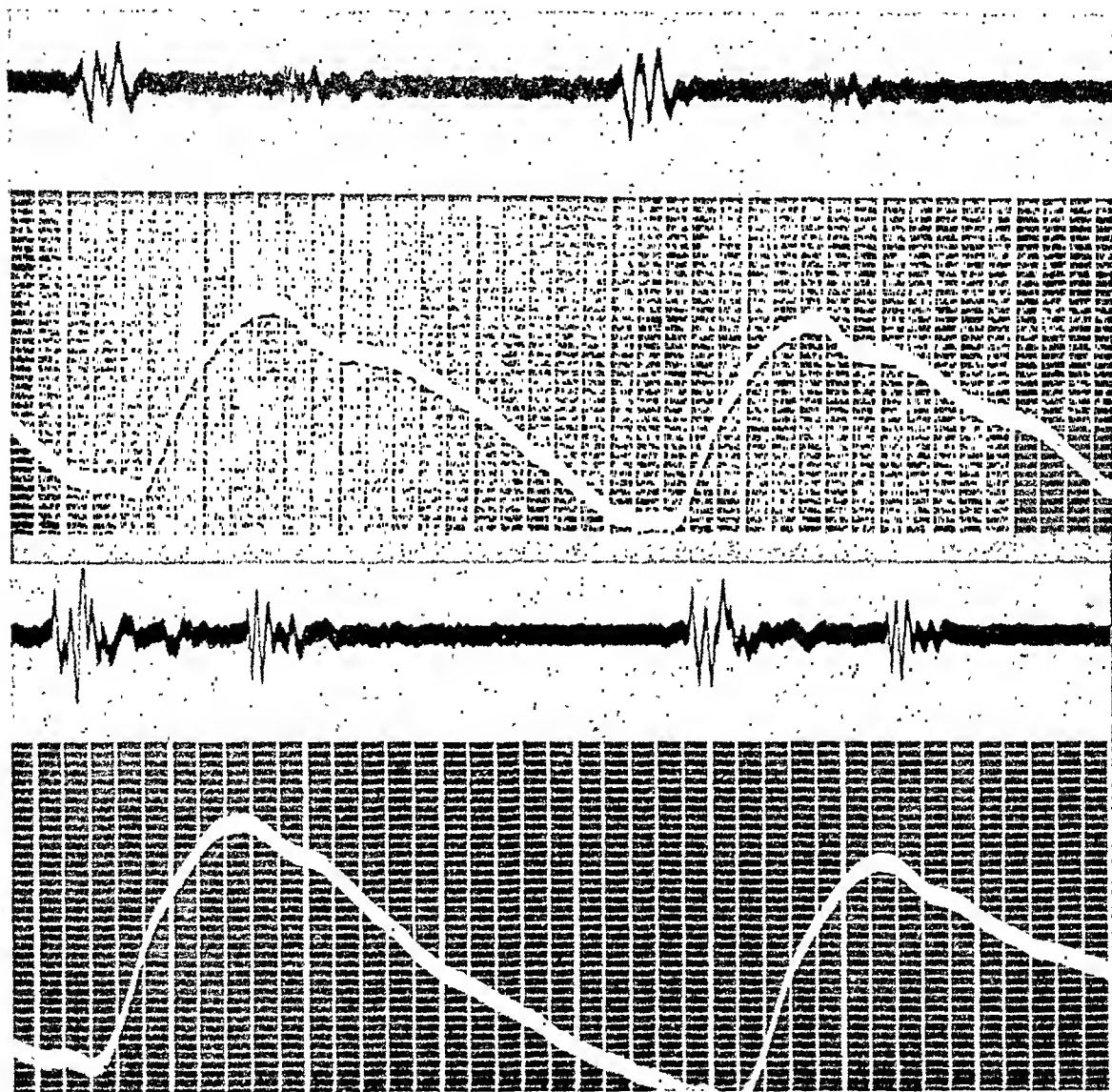


Fig. 8.—Tracings of the aortic arch (Position 6) in two different subjects. The rise of the pulse takes place 0.03 second after the opening of the semilunar valves in both cases. The peak is reached 0.02 to 0.03 second before the closure of the semilunar valves.

Pulmonary Artery (Figs. 9, A and 10, A).—The tracing of the pulmonary arch is usually easily obtained. Occasionally, a large left hilar shadow or a dilated descending aorta may distort the tracing. The pulsations of the latter structures, recorded as densograms in this instance, are of a much smaller amplitude and their influence on the tracing of the pulmonary artery consists only in a smoothing of the waves without other distortion.

The tracing of the pulmonary arch usually fails to show any upward wave during the first part of the first sound-complex. The pulmonic pulsation starts with the opening of the pulmonic valves (second part of the first sound-complex), then rises sharply, and occasionally shows a slight change of the slope which

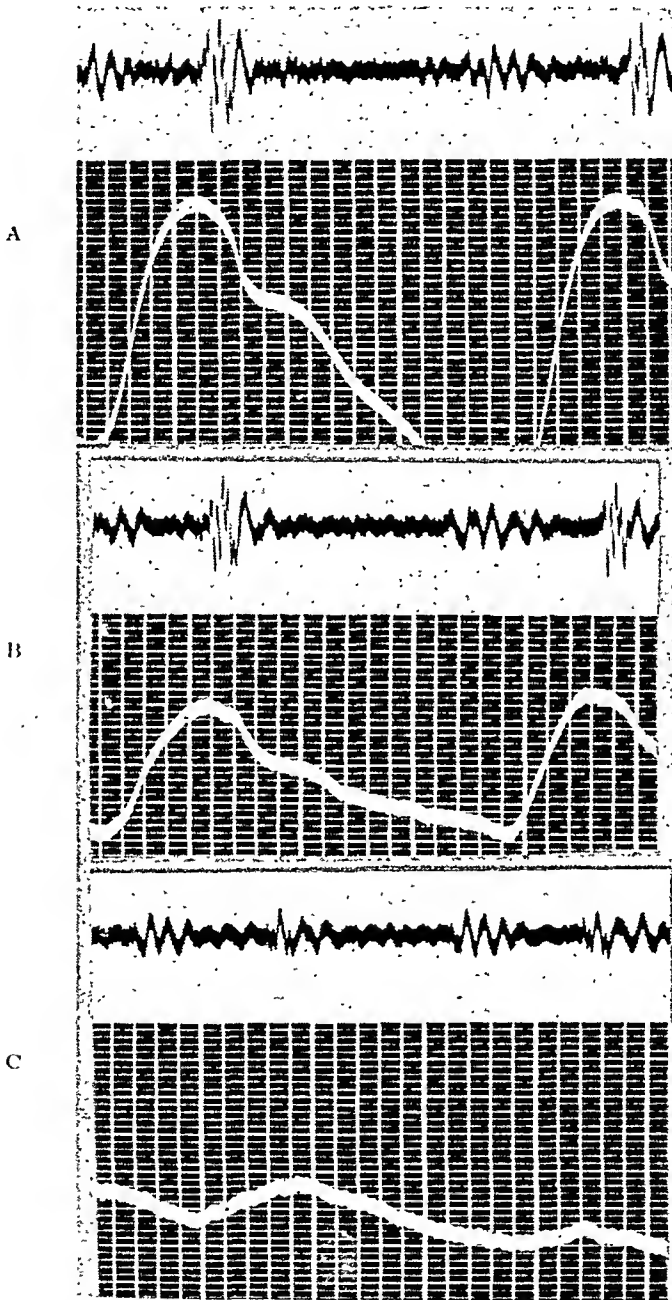


Fig. 9.—Tracings of the pulmonary artery, A, of the right hilar shadow; B, and of the right lung; C, recorded with the same degree of amplification.

is the equivalent of an anacrotic depression. The peak is reached after two-thirds of ventricular systole is completed. The predicrotic notch is usually deep and occurs 0.06 and 0.08 second after the main vibration of the second sound. The dicrotic wave is usually well defined and is higher than that of the aorta.

Its peak is usually from 0.10 to 0.12 second after the main vibration of the second sound. Another positive wave may be seen in late diastole before auricular contraction.

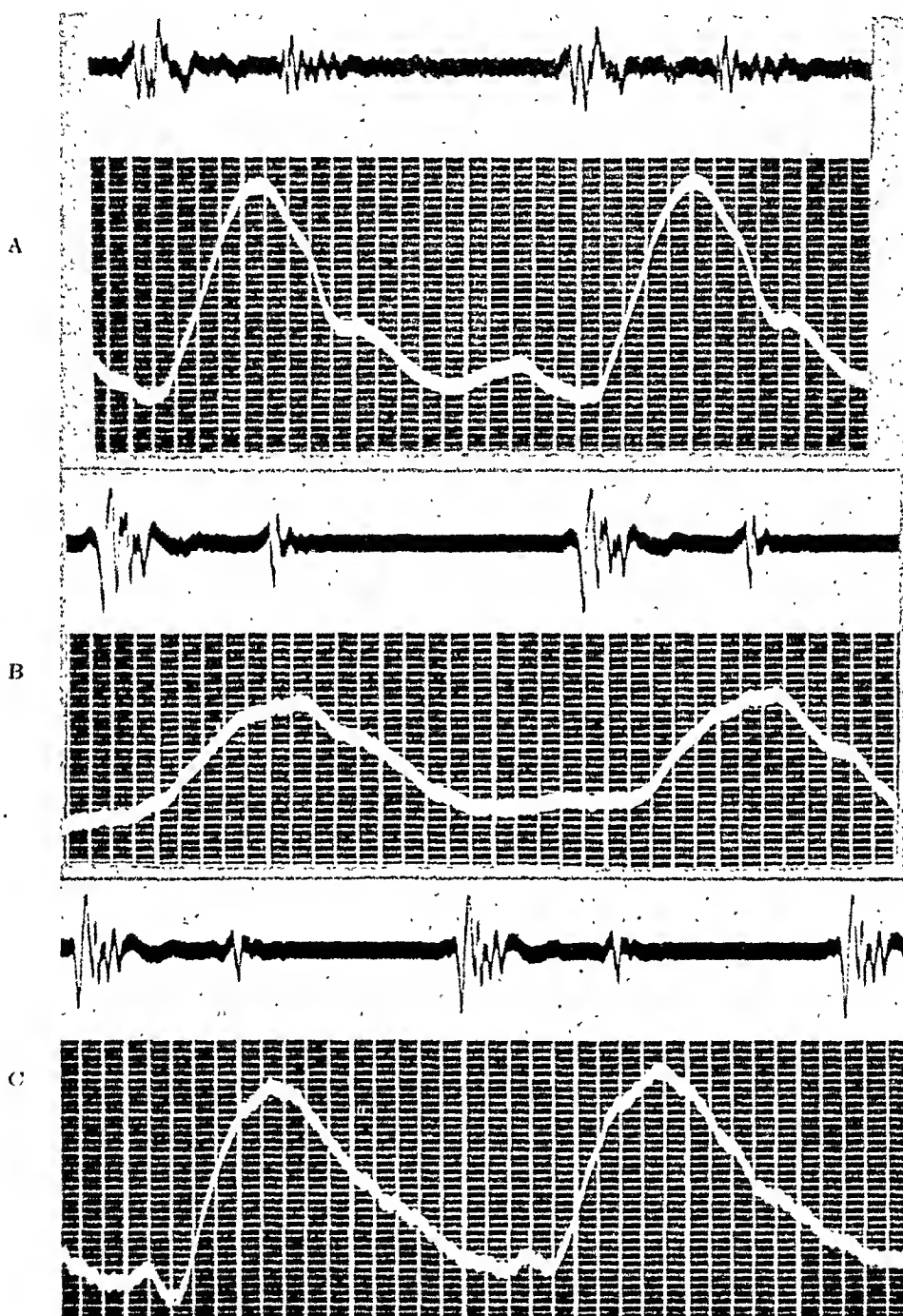


Fig. 10.—Tracings: *A*, of the pulmonary arch (Position 5); *B*, of the right hilar shadow (Position 10); *C*, of the right lung (Position 12). The rise of the pulse takes place 0.02 second after the opening of the semilunar valves in tracing *A*, 0.07 second after it in tracing *B*, and 0.11 after it in tracing *C*. The peak of the pulse occurs 0.06 second before the closure of the semilunar valves in tracing *A*, 0.06 second after this event in tracing *B*, and 0.08 second after it in tracing *C*.

A densogram of the pulmonary arch is easily recorded. The tracing is similar to that recorded with the slit upon the border of the vessel. It may be necessary to record this densogram whenever the contour of the pulmonary artery is obscured by hilar shadows or pulmonary consolidation.

Hilar Shadow (Figs. 9, *B* and 10, *B*).—The tracing of the hilar shadow is a densogram and represents the variations in the opacity of the hilar region caused by changes in the blood content. A comparative study has shown that the amplitude of the normal hilar pulsation is approximately between one-half and two-thirds that of the pulsation of the pulmonary arch. Additional pulsatory phenomena transmitted from the heart and great vessels influence the tracings of the hilar vessels. However, our studies have led us to the conclusion that these influences do not detract from the value of hilar vessel tracings.

When sufficiently amplified, the record of the hilar shadow appears as a typical arterial tracing. The pulsation of this structure occurs approximately 0.04 second later than the pulsations of the pulmonary artery; the rise of the hilar pulse starts approximately 0.12 second after the beginning of the first sound complex. The peak of the pulse wave is reached at the time of or slightly after the main vibration of the second sound. It may be followed by a small notch and then by a small dicrotic wave. In some of the subjects, the main pulse wave is preceded by a negative wave which is synchronous with the peak of the carotid pulse,

While there is no doubt that the positive wave of the hilar pulse signals the arrival of the arterial pulse wave in the branches of the pulmonary artery, one may ask whether the pulsations of the pulmonary veins also influence this tracing. Actually, apart from the smaller depth of both the negative systolic wave and the presystolic wave, some tracings of the right auricle are similar to those of the hilus and lung. However, since the auricular contraction should increase rather than decrease the size of the pulmonary veins, this interpretation is not an acceptable explanation of the presystolic wave. On the other hand, the early systolic depression may be due to the acceleration of the pulmonic venous flow which takes place in that phase.

Lungs (Figs. 9, *C* and 10, *C*).—The densogram of the lung is a tracing which resembles that of the hilus. However, the following differences are present: (a) There is a greater delay in the rise of the pulse wave; this taking place from 0.16 to 0.18 second after the beginning of the first sound-complex, and about 0.04 second after the rise of the pulsation of the hilar shadows. (b) There may be a greater delay of the peak, this occurring from 0.08 to 0.10 second after the main vibration of the second sound-complex. (c) The curve is more rounded and exhibits no trace of either the predicrotic notch or the dicrotic wave.

On the other hand, both the presystolic and the early systolic downward waves, already noted in the hilar tracing, may be present in lung tracings. As changes in the venous content of the lung are also recorded by our tracing, it is possible that these waves, or, at least, their early systolic phase, are influenced by the effect of auricular and ventricular contractions.

A comparative study has shown that the normal hilar pulsation is about one-half the height of the pulsation of the pulmonary artery, and that the pulsation of the lung is about one-half the height of the hilar pulsation (Fig. 9).

Superior Vena Cava (Fig. 11, *A*).—A good tracing of this structure is seldom recorded in normal individuals in either the sitting or the recumbent position.

Occasionally, it is possible to obtain a tracing which resembles the jugular tracing and which shows classically the three positive waves, on which are superimposed smaller vibrations apparently of transmitted origin. The first is an early systolic wave which is sharp and well defined; the second is midsystolic; and the third, extremely variable in position, is a wave which takes place in either early or mid-diastole.

Inferior Vena Cava (Fig. 11, *B*).—This tracing is recorded far more easily than that of the superior vena cava, as long as the subject is able to hold his breath in deep inspiration. The best tracing is recorded with the patient in slight rotation toward the right oblique.

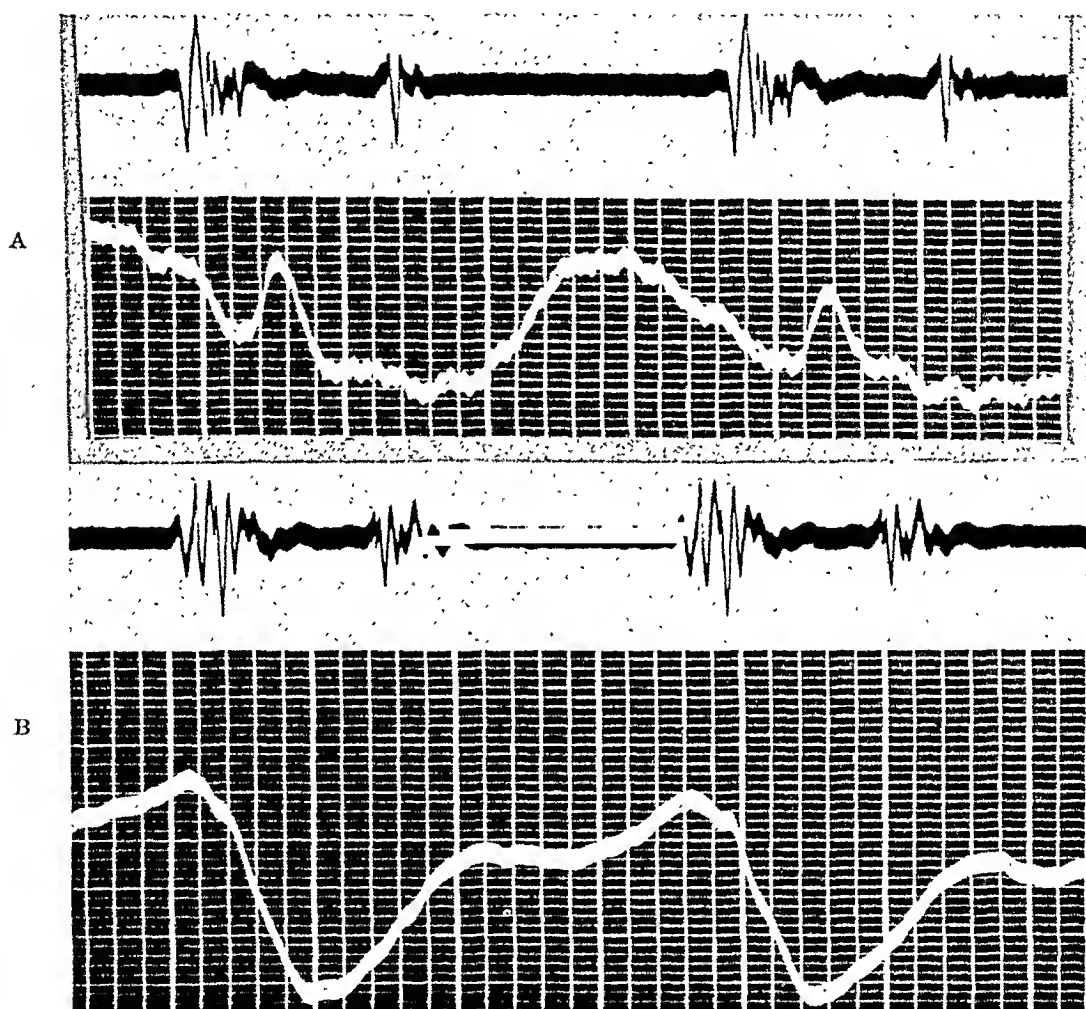


Fig. 11.—Tracings: A, of the superior vena cava in Position 11; B of the inferior vena cava in Position 7.

The inferior caval tracing presents two positive and two negative waves. There is a small presystolic positive wave, apparently due to the slower flow of blood at the time of the auricular contraction (the "a" wave). This is followed by a deep and sharp negative wave at the time of the arterial pulse (systolic collapse). Then follows a slow rise which culminates in a single, or double, peaked wave about 0.10 second after the second sound (the "v" wave). This

apparently is due to the slow engorgement of the vein occurring while the tricuspid valve is closed. The drop which follows occurs after the valve opens. The collapse reaches its maximum depth after the middle of diastole (diastolic collapse). No "c" wave is observed in the tracing of the inferior vena cava.

The tracing of the inferior vena cava is similar to that of the liver in a normal person and is the result of the same physiologic phenomena.

DISCUSSION

Fluorocardiograms show great similarity to tracings recorded on animals in open chest experiments, that is, plethysmograms, intracardiac pressure curves, intra-arterial and intravenous tracings, and suspension curves. In spite of

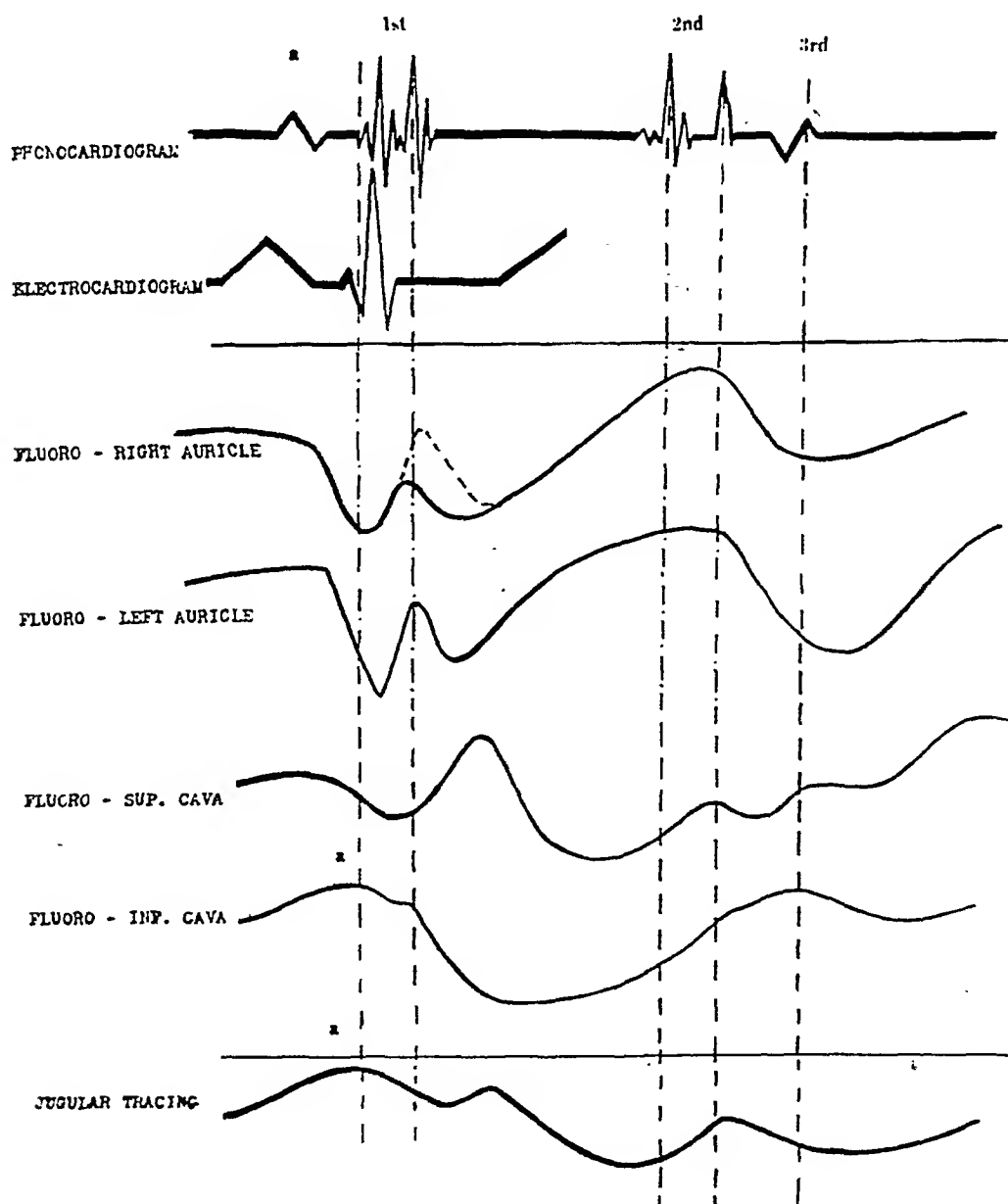


Fig. 12.—Schematic fluorocardiograms of the auricles and large veins and their time relation with various other clinical tracings.

certain limitations of fluorocardiography, due to anatomic and physiologic factors,² the close similarity of these tracings with the established physiologic facts proves the applicability and value of the method.

The timing of the different waves is easily obtained from a phonocardiogram simultaneously recorded. This clinical tracing gives more detail than an arterial tracing, is not modified by slow transmission of the waves (like a jugular tracing), and is more easily and more constantly recorded than a cardiogram.

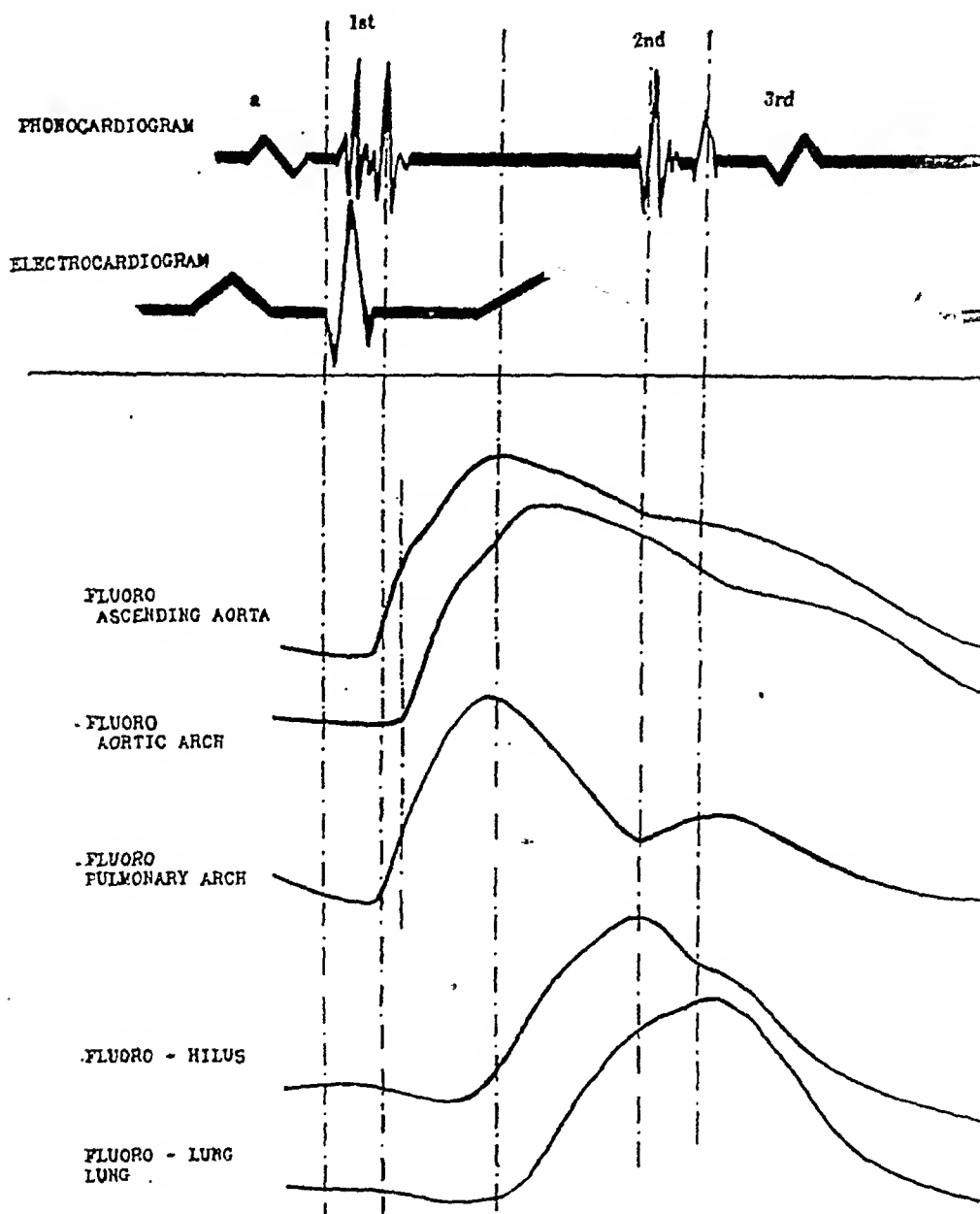


Fig. 13.—Schematic fluorocardiograms of the great vessels and lung, illustrating the time relationship with other clinical tracings.

The use of the electrocardiogram as a timing device is less exact because of the variable time relation between the action currents and the contraction phenomena. The electrocardiogram might have a limited value as a timer in patients with loud or continuous murmurs, but only for the purpose of deciding where ventricular systole begins.

Fluorocardiography permits the study, not only of the motion of cardiac chambers and of the large vessels, but also of certain other structures, such as the medium-sized (hilar shadows) and small (lung parenchyma) pulmonary vessels, and the inferior cava, which have not been accessible by other means.

In the study of the various cardiovascular structures, the following points are considered:

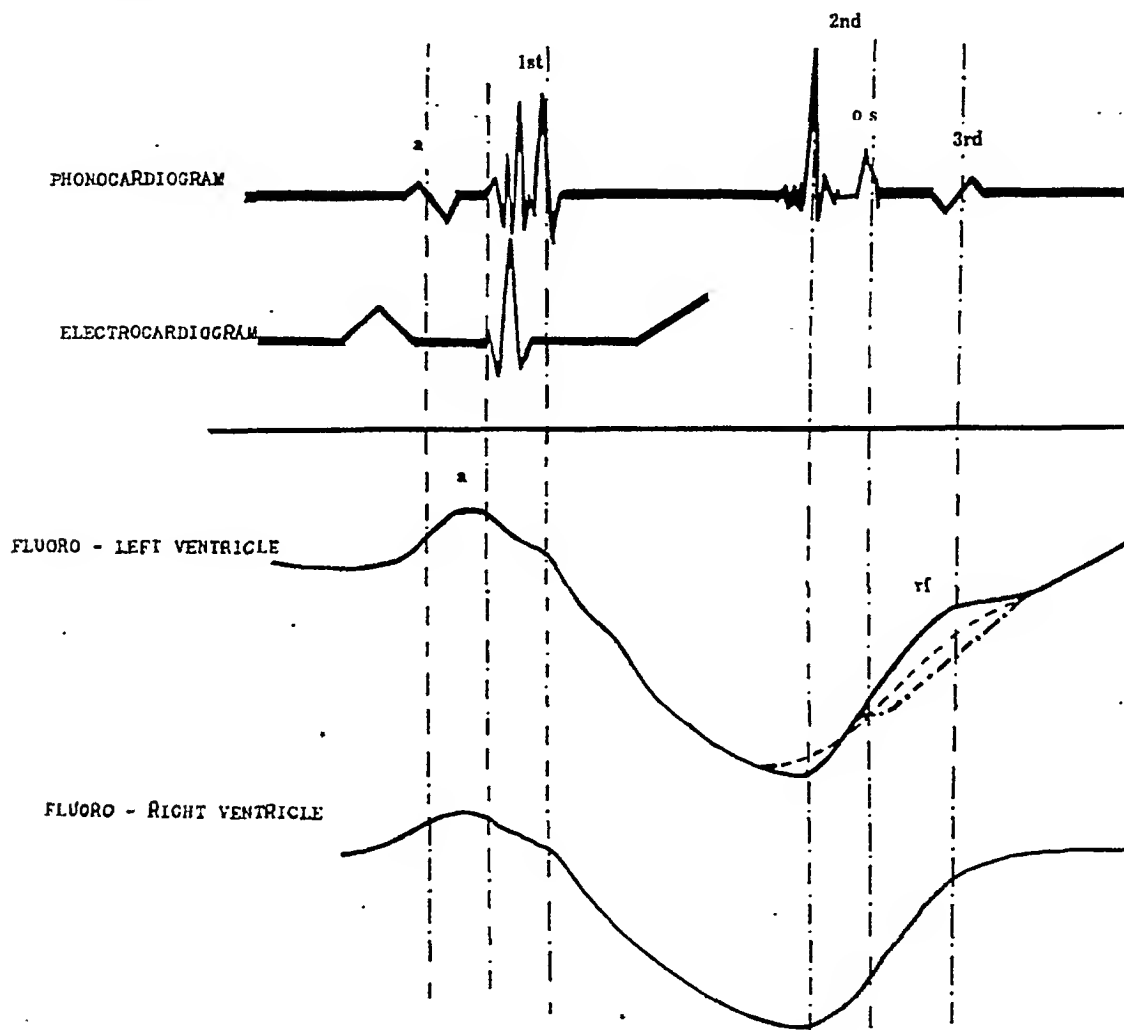


Fig. 14.—Schematic fluorocardiograms of the ventricles and their time relation with other clinical tracings.

(a) *The amplitude of pulsation:* This can be evaluated by comparing the amplitude of pulsations of one structure with that of another, where the pulsations of both structures are recorded with the same degree of amplification.*

(b) *The shape and time of various waves:* These can be evaluated by the use of optimum amplification and by timing the tracing with a phonocardiogram.

(c) *Abnormal movements:* Transmitted and inherent pulsation can be differentiated.

*The degree of amplification can be evaluated by a scale, marking the position of the dial. However, the degree of motion or density change of the cardiac silhouette cannot be expressed in exact numbers. Such a standardizer seems to be within the realm of possibility.

(d) *Dissociation between various chambers* (dissociation between the auricles, bundle branch block, A-V block): This is best accomplished by simultaneously recording the pulsations of the two chambers being studied, using two fluorocardiograms and a phonocardiogram.

Rappaport and Sprague⁵ have shown that the first heart sound is composed of four components. Among these, the following are the most important for timing purposes: (1) a large vibration which occurs at the beginning of the isometric contraction of ventricular systole, and is due to the closure of the mitral and tricuspid valves; (2) another large vibration which occurs at the beginning of the ejection period of ventricular systole, and is caused by the opening of the semilunar valves.

In the second sound, as analyzed by Rappaport and Sprague,⁵ the following vibrations have importance for timing purposes: (1) a group of high vibrations, which are caused by the closure of the semilunar valves at the end of ventricular systole; and (2) a small vibration which is caused by the opening of the mitral and tricuspid valves at the beginning of ventricular diastole.

The coincidence between vibrations of the phonocardiogram and waves of the fluorocardiogram confirms the interpretation of the various waves and vibrations of the sound tracing, as advocated by previous investigators;^{4,5} in particular, it has been confirmed that:

(a) Two different vibrations of the first sound-complex often mark the closure of the A-V valves and the subsequent opening of the semilunar valves.

(b) The main vibration of the second sound-complex is due to closure of the semilunar valves, while the subsequent opening of the A-V valves takes place later and is frequently marked by another small vibration.

(c) The third sound is due to the rapid filling of the ventricles in early diastole.

Figs. 12, 13, and 14 have been constructed on the basis of our tracings in order to facilitate comparison.

SUMMARY AND CONCLUSIONS

Fluorocardiograms (electrokymograms), recorded over various cardiovascular structures, have been studied in twenty normal subjects. These tracings are compared with simultaneously recorded phonocardiograms.

The identification of the various waves and their relation to the phases of the cardiovascular dynamics are discussed. They may be attributed to two different phenomena: (1) motions of the x-ray silhouette caused by changes in volume in systole and diastole, and (2) motions due to rotation, traction, or total shift due to contraction or dilatation of either the same or some other cardiovascular structure.

The tracing of the apex reveals a small positive wave due to completion of filling as the effect of auricular contraction, a small subsequent notch and a deep negative wave in systole, a rapid rise in early diastole, and a slow rise later.

The causes of these phenomena are discussed. The possible lack of coincidence between the deepest point of the systolic wave and the second sound is attributed to displacement of the ventricular mass. Tracings recorded over any other point of the left ventricle give smaller waves and a faithful expression of ventricular systole. The same is true for the right ventricle, whose contraction can be recorded in the lateral positions.

Both left and right auricular tracings reveal first the results of auricular contraction, then a decrease of auricular volume due to ventricular traction over the A-V septum, and later a collapse in early diastole. The causes of the three negative waves are analyzed.

A tracing of the ascending aorta is possible in the left oblique position and occasionally, in the posteroanterior position. It is recorded in the latter position in older people because of atherosclerosis and dilatation of the aorta.

The tracing of the aortic knob has all the characteristics of a "central" pulse; that of the pulmonary knob presents a smaller anacrotic depression and a higher dicrotic wave, often resembling the tracing of a peripheral pulse.

The tracings of the hilar shadows and of the lung parenchyma are analyzed and discussed. They reveal a slowly moving arterial pulse in the pulmonary circulation.

A good tracing of the superior vena cava is seldom recorded in normal subjects, either young or old. It is more commonly recorded if there is venous engorgement. On the other hand, the tracing of the inferior cava is obtained frequently. It shows a positive wave in presystole, a deep systolic collapse, and a diastolic collapse. It resembles the liver tracing of a normal subject.

A widely accepted interpretation of the phonocardiogram is confirmed by fluorocardiography.

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Errata

In the January, 1948, issue of the JOURNAL, Fig. 1, p. 135, and Fig. 2, p. 137, were inserted upside down in the article entitled "Paroxysmal Auricular Tachycardia at a Rate of 86 Per Minute," by Ralph Miller, David Biber, and Julius S. Perelman.

In the article entitled "Reactions to Decholin as Used in Circulation Time Determination" by James J. Norman, which appeared in the November, 1947, issue of the JOURNAL, the described reactions were incorrectly attributed to "Decholin." Actually, the material used was Sodium Dehydrocholate Solution, manufactured by Lederle Laboratories, Inc., New York, N. Y., and not the product manufactured by the Ames Company of Elkhart, Ind., (which now owns the trademark "Decholin") or Riedel-de Haen, Inc., New York, N. Y.

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THE FEBRUARY ISSUE

The Editorial Board and the C. V. Mosby Company are delighted to be able to devote this entire issue to the scientific papers presented at the last Annual Meeting.

The preparation and publication of a large special issue is not yet a simple matter. In spite of the difficulties, all papers, except those which have been published already or are to be published elsewhere, are being included in the approximate order of their presentation.

The special preparation which some of the papers have required prevents their presentation in this issue. These postponed papers, which will appear in subsequent issues, include The George Brown Memorial Lecture, given by Dr. Helen Taussig and Dr. Alfred Blalock, and the presentations of Dr. Joseph T. Roberts, Dr. Myron Prinzmetal and associates, Dr. John Schweppe and associates, and Doctors Harold K. Moss and Louis G. Herrmann.

The necessity of omitting the Discussions is regretted.

MEETING OF THE INTER-AMERICAN SOCIETY OF CARDIOLOGY

The Inter-American Society of Cardiology has authorized the meeting of the III Inter-American Cardiological Congress, to be held in Chicago, Ill., at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting, the week of June 20. Inquiries regarding the Congress may be addressed to the offices of the III Inter-American Cardiological Congress, at the Michael Reese Hospital, Chicago, Ill.

ANNUAL MEETING

The Annual Meeting and Twenty-first Scientific Session of the American Heart Association will be held in Chicago, Illinois, on June 18 and 19, 1948. The Stevens Hotel will be the headquarters for all meetings and for the Annual Dinner which will take place on Saturday evening, June 19.

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No. 3

Original Communications

THE EFFECT OF OCCLUSIVE ARTERIAL DISEASES OF THE EXTREMITIES ON THE BLOOD SUPPLY OF NERVES. EXPERIMENTAL AND CLINICAL STUDIES ON THE ROLE OF THE VASA NERVORUM

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WITH THE TECHNICAL ASSISTANCE OF W. H. JARVIS, R. S. BROWNE,
F. D. SPENCER, JR., JULIAN KEY, J. A. RIVAS, AND D. BRANDT

ISCHEMIA of peripheral nerves has received little attention from physicians. Except as a nerve may reflect changes in the skin, muscles, and nerve endings affected by ischemia, the blood supply of peripheral nerves has been thought to be of little importance by most physiologists. The anatomy of the blood supply of nerves has been described by many authors, but even this knowledge is not generally recalled in connection with clinical problems. It is common belief that the metabolism of a peripheral nerve depends upon the cell bodies of its neurones rather than upon the nourishment of its axones.

For about twelve years, I¹⁻⁴ have been studying the problem of the role of the vasa nervorum under both clinical and experimental conditions. The find-

The work described in this paper was done in part under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Texas. The illustrations and sections were made at the Army Institute of Pathology.

Presented at the Twentieth Scientific Meeting of the American Heart Association, Atlantic City, N. J., June 6 and 7, 1947. (Also, in part, before the Galveston County, Texas, Medical Society on Oct. 31, 1941, and Feb. 8, 1943; the Medical Society of the District of Columbia as the Davidson Lecture, Oct. 17, 1945; the Society for Experimental Biology and Medicine, Washington, D. C., Dec. 6, 1945; the American Association of Anatomists, Cleveland, Ohio, April 6, 1946; and the American Medical Association, Section on Nervous and Mental Diseases, Atlantic City, N. J., July 11, 1947.)

From the University of Arkansas School of Medicine, Department of Medicine, Little Rock, Ark. The earlier work was conducted at Gallinger Municipal Hospital, Georgetown University, George Washington University, Washington, D. C., and the University of Texas Schools of Medicine, Galveston, Texas.

ings indicated that ischemic nerves suffered changes in function and structure. After our work was well under way, several publications of importance in this field appeared in this country and abroad, stimulated possibly by the interest in injuries of peripheral nerves in war casualties.

Aviation and submarine aeroembolism suggested certain techniques to me. My experiments have consisted of interference with the blood supply of peripheral nerves in various ways under both acute and survival conditions. Clinical cases have been collected where the influence of ischemia on a peripheral nerve could be demonstrated by dissection and injection.

EXPERIMENTAL STUDIES

Acute Experiments.—Confirmation of previous reports concerning the anatomy of the blood supply of normal peripheral nerves was obtained by injecting dye (either Chicago blue, 2 per cent, or India ink diluted with equal parts of saline) into the aorta of normal dogs at pressures of 100 to 120 mm. Hg before sacrificing the animal. The nerves were then carefully removed and fixed in 10 per cent formalin. Also, nerves from the normal limbs of the dogs with experimental lesions were studied in the same way. It was found by clearing and dissection that there is a rich blood supply to each nerve (Figs. 1 and 3,4). This blood supply consists of a finely meshed plexus of capillaries, precapillaries, arterioles, and venules distributed longitudinally in the perineurium within the central part of a nerve and between the axones. This intrinsic plexus arises from another coarser plexus in the epineurium or fibrous sheath that surrounds the nerve. This coarser plexus corresponds to the plexus in the pia mater of the spinal cord and brain. It consists of one or sometimes more coarse longitudinal vessels anastomosing with segmental nutrient arteries which come from blood vessels in the neighborhood. Thus, there is both a longitudinal and segmental arrangement of the blood vessels in the epineurium. The origin of the nutrient arteries from neighboring vessels is subject to variation in different cases. Veins accompany the arteries. The nutrient arteries and some of those within the nerve have a well-defined muscular media, suggesting that the flow of blood through the vasa nervorum is subject to vasomotor autonomic control. The distance between the nutrient arteries also varies, but is usually between one and three inches for the larger named nerves. With smaller nerves, the segmental vessels enter at shorter intervals. Every nerve is nourished by small vessels. Even a single strand nerve in the skin is accompanied by a capillary network; this was seen in a transparent chamber grafted (for "visualization" of vessels and nerves) into a rat's back by Dr. G. H. Algire, of the National Cancer Institute.

To occlude the blood supply of a peripheral nerve, several procedures which would impair the blood supply in ways simulating clinical conditions were applied to the sciatic nerve of normal adult dogs (Fig. 2). Control experiments consisted of exposing a sciatic nerve in exactly the same way as in these procedures but with omission of the devascularizing procedure. In five such control experiments no changes from normal were found on testing the function of



Fig. 1.—The larger vasa nervorum filled with graphite suspension which was injected into a segmental nutrient artery. Note the epineural plexus, longitudinal channels, and deeper, smaller anastomosing vessels. (Dog's sciatic nerve, cleared.)

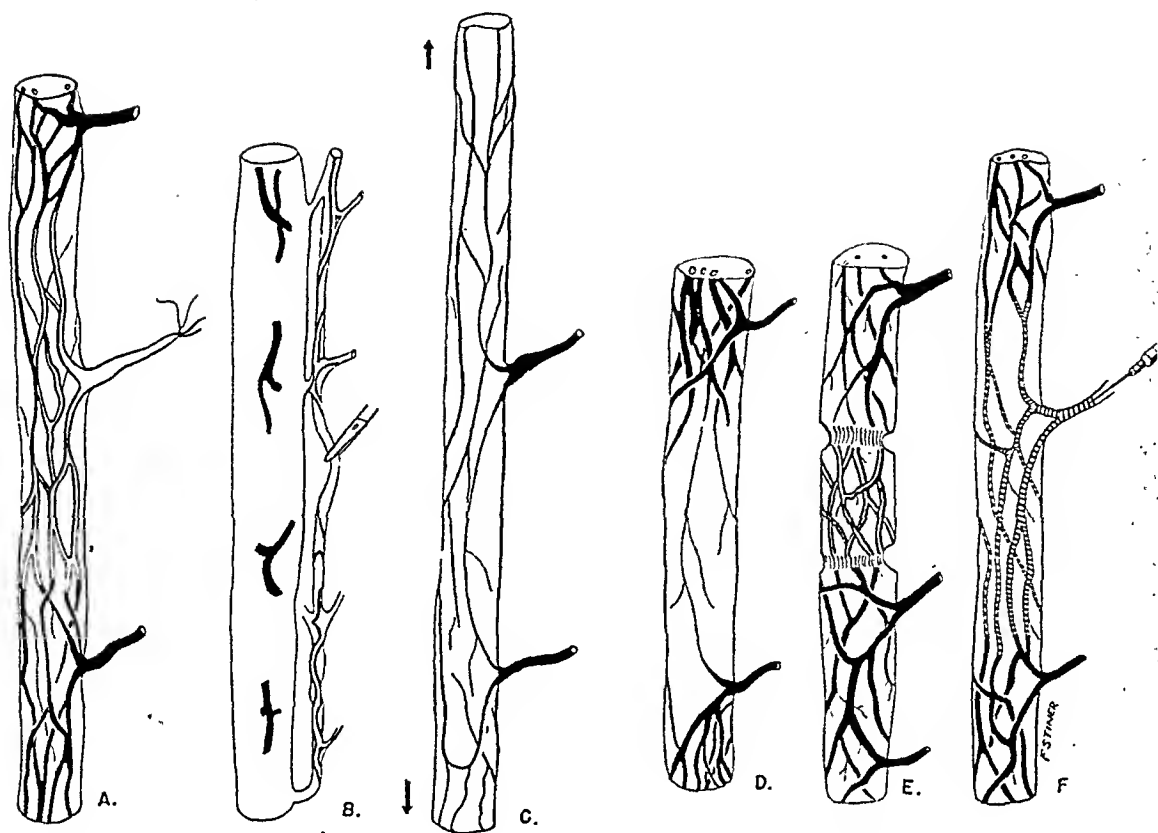


Fig. 2.—Diagrams of procedures for producing ischemia of nerves by obliterating the vasa nervorum. A, Ligation of a nutrient artery. B, Stripping the epineurial plexus. C, Stretching a nerve. D, Tourniquet. E, Compression by two ligatures or pinching with hemostats. F, Embolism by injecting *Lycopodium* spores, graphite, or air.

the nerve, in the sections, or in the degree of injection by dye. The devascularizing experiments were as follows:

(1) *Ligation of a Segmental Nutrient Artery* (Figs. 2,A and 3,B and C): As in all of the following experiments, the sciatic nerve was exposed by careful dissection during anesthesia with nembutal given intravenously. The field was kept moist with normal saline at 37° centigrade. A segmental nutrient artery was divided between ligatures without any trauma or handling of the nerve. Chicago blue dye was then injected into the aorta and the animal was sacrificed. Before injection of the dye, no change in the function of the nerve was demonstrated when the tendon reflexes and response to heat, pinching, or electrical stimulation of the nerve were tested.

As shown diagrammatically in Fig. 2,A and in the photographs in Fig. 3,B and C, the blue dye filled the vasa nervorum in this region with a patchy irregular distribution. In the region of the nerve supplied by the ligated segmental nutrient artery, blood remained in a number of the vasa nervorum, giving an intermingled red and blue coloration of the nerve.

Histologic sections showed no constant abnormalities.

(2) *Stripping the Perineurium* (Figs. 2,B and 3,D and E): In other animals, the left sciatic nerve was carefully exposed by the method previously de-

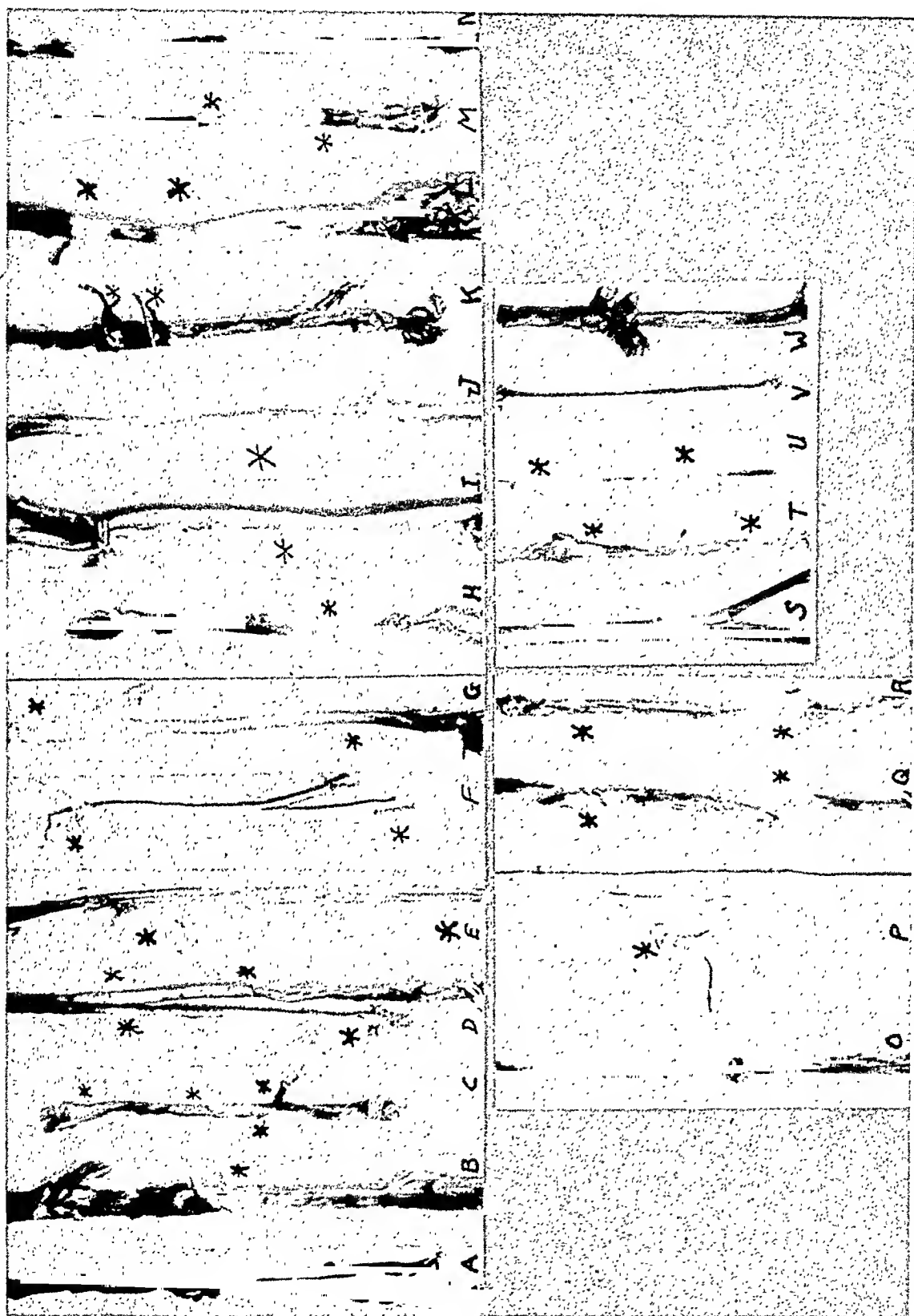


Fig. 3.—Vasa nervorum in normal and ischemic sciatic nerves (dogs), injected through the aorta with dye. A, Normal. B, Nutrient artery tied. C, Four nutrient arteries tied. D, E, Epineurium stripped off. F, G, Nerve stretched. H, I, J, Constricted by tourniquet around thigh. K, L, Ischemia between ligatures 10 and 20 mm. apart. M, Ischemia between levels pinched by hemostats. N, O, Normal. P, Embolism by *Lycopodium* spores in sciatic branch of inferior gluteal artery. Q, R, Atherosclerosis of vasa nervorum. S to W, Segmental ischemia from embolism of left femoral artery by spores. S, Normal left sciatic nerve. T, Ischemic left common peroneal nerve. U, Ischemic left femoral nerve; V, normal right femoral nerve; W, normal right sciatic nerve. (Lesions marked by *.)

scribed and its perineurium stripped away very carefully with finely pointed forceps. Pinching or stretching the nerve fibers inside the epineurium was avoided. The blood vessels in the epineurium were pinched away in such a way as to cause no visible hemorrhage in the nerve. In these twelve animals where the epineurium was stripped away over a distance varying from 1.0 to 3.0 cm., no change was noted on testing tendon reflexes, sensibility to heat, pinching, or electrical stimulation.

When dye was injected into the aorta, the nerve was quite ischemic on its surface in the region from which the epineurium had been removed. Because of the presence of blood supply in the central part of the nerve, as a result of the longitudinal anastomoses above and below, there was a patchy and variable amount of dye in the stripped segment.

This experiment indicated that the plexus of vessels in the epineurium is important for maintaining an intact blood supply in a nerve, but that partial vascularity may be retained despite its absence over a short segment.

(3) *Stretching the Nerve:* In six dogs the left sciatic nerve was stretched in its longitudinal axis by traction upon the lower limb after all structures at the knee joint had been severed with the exception of the nerve, the popliteal artery, and its accompanying vein. Spreaders were placed between the femoral condyles and the tibial head so that these two structures were separated by a distance of one to two centimeters. Dye was then injected into the aorta and the animal sacrificed.

The vasa nervorum of the left sciatic nerve were obliterated by the stretching so that no dye entered the stretched segment (Figs. 2,C and 3,F and G). This ischemic or uninjected stretched nerve, when compared with the normally injected nerve of the opposite limb, as was done in the other experiments, showed a very striking difference in color. The stretched nerve was white, the normal one blue. Some of the small side branches of the sciatic nerve were not stretched by the procedure, because of the angle of their branching, and they were well injected. After the stretching was released during removal of the nerve for clearing, some dye flowed into the previously stretched vasa nervorum, apparently due to the effects of capillary pressure in these small vessels.

This experiment showed that the vasa nervorum may be obliterated by stretching, just as the lumen of a rubber tube may be occluded by stretching the tube.

(4) *Constriction by a Tourniquet:* In six animals a tourniquet of rope one-fourth inch in diameter was placed around the middle of the right thigh in such a way as to compress all structures at that level except the femoral artery and vein, which were outside of the tourniquet. The tourniquet was then tightened and dye was injected into the aorta before the animal was sacrificed.

The cleared nerve from this extremity was uninjected or ischemic at the level inside the tourniquet and poorly injected or partly ischemic for several centimeters above and below the constriction (Figs. 2,D and 3,H and J).

These experiments showed plainly that the blood supply of the nerve can be obliterated effectively by compression of the limb with indirect pressure upon the nerve itself. Such pressure resembles that on a nerve in a patient who has a tumor, adhesion, dislocation, arthritic spine, faulty posture, or other condition where pressure on a nerve obliterates its blood supply.

(5) *Constriction of the Nerve:* Two ligatures were tied around the left sciatic nerve at intervals varying from 10 to 30 mm. in seven dogs. In some cases, a split rubber tube was placed around the nerve under the ligatures to prevent cutting of the nerve. Various degrees of constriction of the nerve were used.

Dye injected into the aorta filled the vasa nervorum of the nerve above and below the segment between the ligatures (Figs. 2,*E* and 3,*K* and *L*) as well as in the normal nerve of the opposite limb. No dye entered the vasa nervorum between the ligatures even in the specimens where the constriction with the ligature was slight. Between the ligatures, red blood was trapped, causing the opacity between the two ligatures seen in the photographs.

In three other animals the left sciatic nerve was clutched between the jaws of a hemostat at two points preceding the injection of dye into the aorta. Although the hemostats had been removed before the injection, no dye entered the vessels of the nerve between the two points clutched with the hemostat (Figs. 2,*E* and 3,*M*).

These two types of experiments indicated that the blood supply of a nerve can be destroyed by interference with the longitudinal anastomoses in the nerve, and that constriction of a nerve can obliterate its blood supply.

(6) *Embolism of the Vasa Nervorum:* The vasa nervorum were occluded by injecting a nutrient artery of the left sciatic nerve with emboli of particulate material. This consisted of Lycopodium spores,* powdered graphite, or air. In each case the emboli filled the small blood vessels within the central part of the nerve as well as in the epineural vessels and the nutrient arteries. When dye was injected into the aorta, none of it reached the portion of the nerve supplied by the obliterated vasa nervorum.

In seven dogs, when the suspension of Lycopodium spores was injected into the left inferior gluteal artery (ligated above and below the origin of its nutrient artery to the nerve to prevent embolization of collateral vessels), the nearby portion of the left sciatic nerve became devoid of blood, became white, and remained so even after injection of the blue dye into the aorta (Figs. 2,*F* and 3,*P*).

When air was injected into the nutrient blood vessels of a sciatic nerve in five dogs, the discoloration after the aortic injection of dye was very patchy and irregular (Figs. 2,*F* and 3,*Q* and *R*), as contrasted with a homogeneous discoloration of a normal nerve and the complete absence of dye in the nerve after devascularization by Lycopodium spores or other emboli. Five large white rats were placed in a chamber with pressure simulating an altitude of 12,000 feet.

*A freely flowing suspension of Lycopodium spores was prepared by shaking the spores in ether for a few minutes, filtering, and then suspending the spores in five to ten parts of normal saline. This prevented the adherence of the spores and blocking of the syringe as encountered otherwise.

When they were removed and the sciatic nerves rapidly exposed, the vasa nervorum were filled with small bubbles of gas.

These two experiments showed that aeroembolism can obstruct the vasa nervorum.

In another dog (Fig. 3, *S, T, U, V, and W*), *Lycopodium* spores were injected into the left external iliac artery. As a result, there was obliteration of the vasa nervorum of the left femoral nerve and of the left peroneal and other nerves below the knee which derived their blood supply from the popliteal and other branches of the femoral artery. However, the left sciatic nerve was as well injected with dye as were the right sciatic, the right femoral, and other nerves of the normal opposite limb.

This result was of value in showing that the longitudinal anastomosis within the sciatic nerve was inadequate for maintaining nourishment to the nerves below the knee, although apparently adequate for nourishing the nerve between the knee and hip joint under these circumstances.

Survival Experiments.—In twenty-three dogs the left sciatic nerve was exposed during anesthesia with nembutal, and procedures of the types which have been described were carried out aseptically; every effort was made to avoid injury to the nerves or surrounding structures. After replacing the muscle and closing the skin, the animal was allowed to recover consciousness and survive for one to seven weeks before dye was injected into the aorta and the animal sacrificed. During the survival period the functions of the nerve were frequently tested.

Results with several methods of attempting chronic devascularization of nerves were as follows:

(1) *Ligation of Nutrient Arteries:* In five dogs, when only a single nutrient artery or part of the nutrient arteries between the hip and knee joints had been ligated, no clinically discernable evidence of dysfunction of the sciatic nerve was found. In three dogs, when all nutrient arteries coming to the sciatic nerve between the hip and knee joints were destroyed, weakness of the extensor muscles of the foot and hamstring muscles was noted. Changes were not as marked, however, as in the studies which will be described. Histologic study revealed only occasional degenerated axones, especially near the periphery of the nerves.

(2) *Stripping of the Perineurium:* When the epineurium had been carefully stripped away for only 1.0 to 3.0 cm. in five dogs, no changes in function of the nerve were noted. When the epineurium was stripped away from all or most of the segment of nerve between the hip and knee joints in four dogs, impaired function of the nerve was shown by weakness of the extensor muscles of the foot and in the hamstring group of muscles, by footdrop with trophic ulcers on the dorsal surface of the foot, and by partial or complete loss of sensibility to pinpricks, pinching, or heat. Histologic study revealed degeneration of many axones, especially those with large myelinated sheaths; axones near the periphery of nerve bundles were affected more than those in the central part of the nerve.



Fig. 4.—Hind limbs one week after embolism(spores) of left sciatic vasa nervorum. A, Trodop, inverted foot, atrophied calf and hamstring muscles, necrotic spots on skin. B, Trophic ulcers on dorsum of toes. C, Hyperflexed ankle.

(3) *Stretching of the Nerve:* No survival experiments of this type were completed. Because it was not possible to obtain longitudinal stretching of the nerve without severing the knee joint, studies during survival would have been difficult to evaluate. Stretching of the nerve by lateral displacement was performed but the results were equivocal because injury might have been done to the axones of the nerve and also because the blood supply returned to the nerve after stretching was released and the nerve allowed to shorten to its original length.

(4) *Compression of the Nerve:* For the reasons just stated, studies were not made during survival after clamping the nerve with hemostats or compressing it by ligature or tourniquet. In such experiments, we could not distinguish between the effects of injury to the axones and injury from anoxemia or ischemia.

(5) *Embolism of the Vasa Nervorum:* In seven dogs in which obliteration of the vasa nervorum was obtained by injection of sterile graphite or Lycopodium spores into the nutrient artery of the left sciatic nerve, evidence of impaired function of the nerve was found as soon as the animal recovered from the anesthesia. In these animals, loss of strength of the hamstring muscles of the thigh, the leg muscles, and those of the foot was so great that the animal (Fig. 4) seldom tried to use the affected limb for running except when fatigue made it necessary. Likewise, sensibility to painful pricking, pinching, or heat was lost over the area supplied by the branches of the devascularized sciatic nerve. Patellar reflexes were hyperactive and ankle jerk reflexes were absent. After intervals of a few days to two weeks, loss of tone and severe wasting of the muscles supplied by the devascularized sciatic nerve became evident, as did the appearance of trophic ulcers on the dorsum of the left hind foot due to pressure from running or standing on the left extremity after the development of the toe drop (Fig. 4,B). Vesicles and spots of dry gangrene developed in the skin of the dorsolateral aspect of the thigh adjacent to and below the incision and also of the leg. These changes were thought to be due to loss of innervation of the skin from branches of the sciatic nerve. Another less likely possibility is that the emboli passed into the small blood vessels of the skin through anastomoses with the other nutrient arteries.

When these animals were sacrificed during injection of blue dye into the aorta, nerves were uninjected in the region below the earlier devascularization by embolic material. Histologic examination revealed degeneration of the nerve below this site just as though the nerve had been cut.

CLINICAL OBSERVATIONS

Evidence of obstruction of the vasa nervorum was found in patients suffering from a wide variety of conditions, either by inspection of the dissected nerves or after injection of dye into the popliteal artery of limbs amputated from necessity. Examples of such cases follow:

(1) A patient with subacute bacterial endocarditis showed numerous embolic phenomena affecting the brain, lungs, kidney, spleen, eye, and skin, and developed foot drop with evidence

of paralysis of the left peroneal nerve. There was also impaired sensation to touch, pain, temperature, and vibration on the lateral aspect of the left foot and toes. Autopsy revealed large friable vegetations on the mitral valve with infarctions in the organs named. Careful inspection of the left peroneal nerve revealed petechiae and thrombosis of the vasa nervorum in the middle of the nerve, due to obstruction of the nutrient arteries of the nerve by a small embolus.

(2) A woman with a one-year illness of unknown cause had had septic fever, severe anemia, weakness, and cachexia for several months. Several days before death, she suddenly developed an inability to flex the left hip joint and extend the left knee. At autopsy the only abnormalities found were a small denuded roughened area of the mitral valve which resembled the base from which a vegetation had been separated recently and a hemorrhagic area 2.0 cm. long in the left femoral nerve. The nutrient artery supplying this section of the nerve was occluded by a small embolus. This embolus was part of the vegetation which had broken away from the mitral cusp.

(3) During repair of a man's right femoral hernia, injury to a nearby nutrient artery of the femoral nerve occurred. This nutrient artery was divided between ligatures. After recovery from anesthesia, the man was unable to extend his right knee and had no sensation for touch on the anterior right thigh for five weeks, after which time these functions gradually returned. The injury to the blood supply of the right femoral nerve accounted for these defects.



Fig. 5.—Thrombosed vasa nervorum of left plantar nerve, with degeneration of nerve fibers. Case 4.

(4) A man with myocardial infarction suddenly developed pain in the large toe and medial portion of the foot. These parts became pale followed by reddish purple discoloration. Pain as well as the power of sensation disappeared two days later. Despite paravertebral lumbar sympathetic block with novocaine and refrigeration therapy, gangrene of the toe and foot developed which required mid-thigh amputation. Careful dissection of the vessels and nerves revealed embolism and thrombosis of the dorsalis pedis and medial plantar arteries, with thrombosis of the anterior tibial artery and the accompanying veins. Thrombosis of the vasa nervorum of the medial plantar nerve was also found (Fig. 5). These findings indicated that the initial pain was due to partial or early ischemia of the involved nerves, with disappearance of pain and sensation after the thrombosis of the vasa nervorum had become complete or had endured long enough for degeneration of the axones to occur.

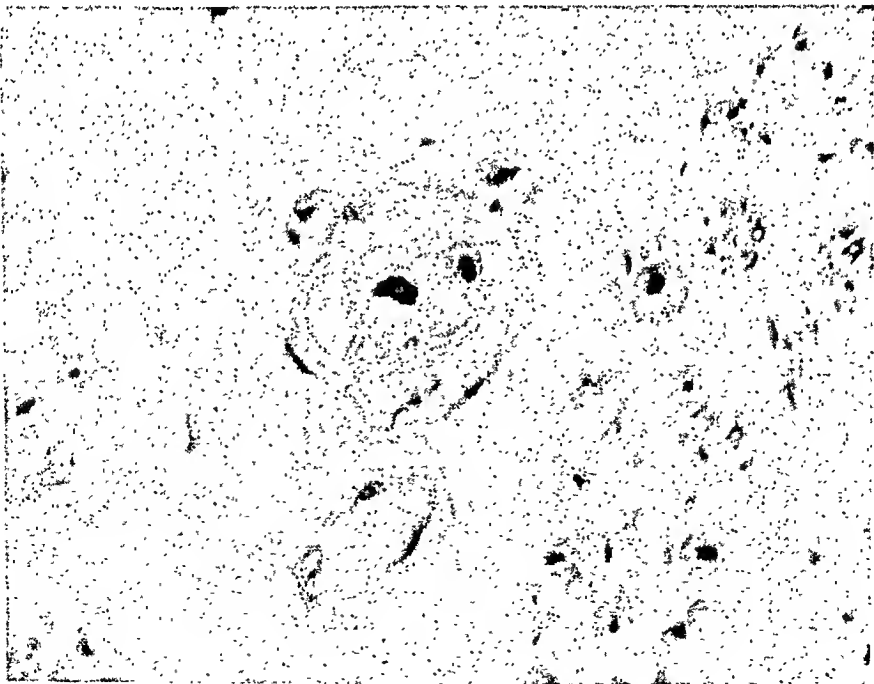
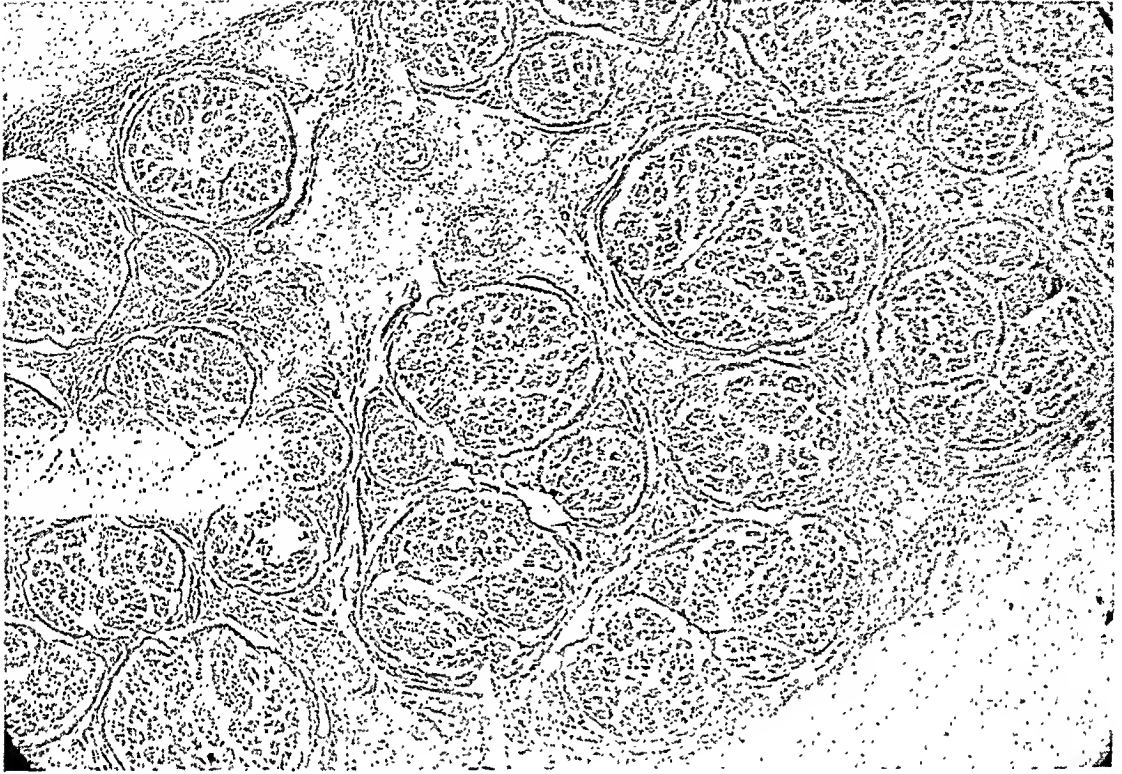
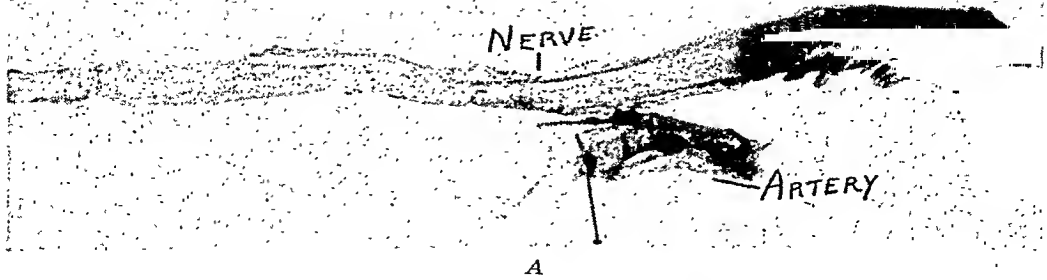
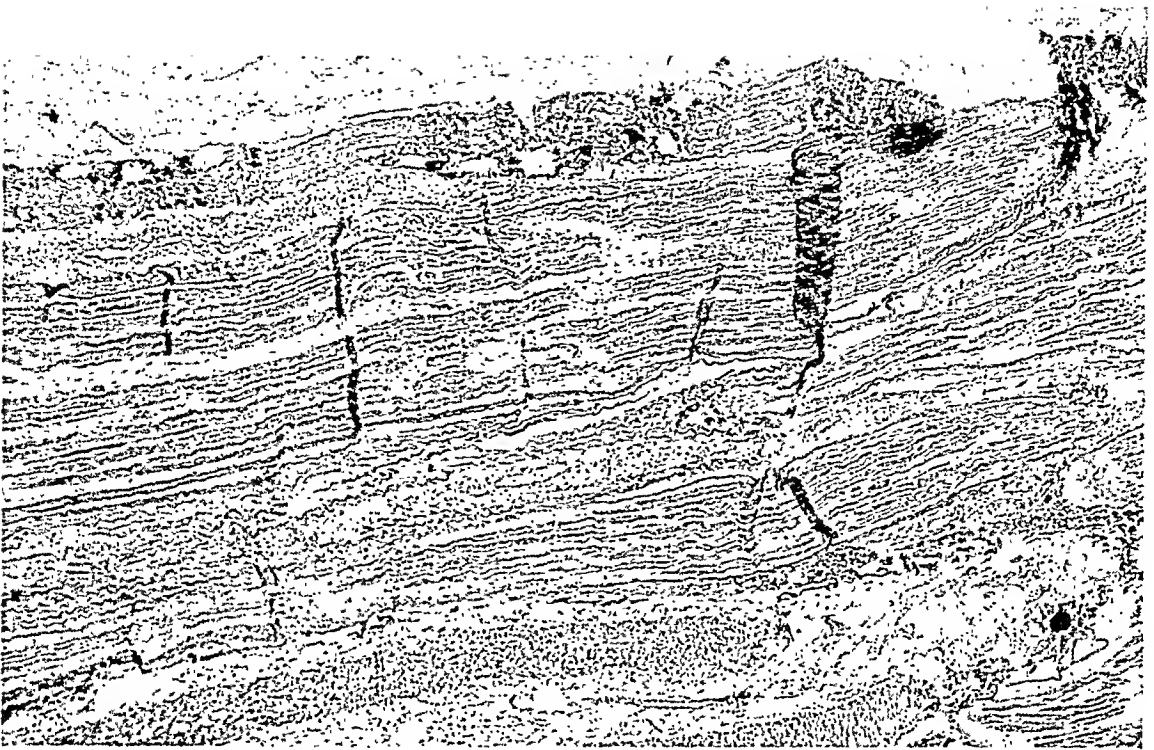
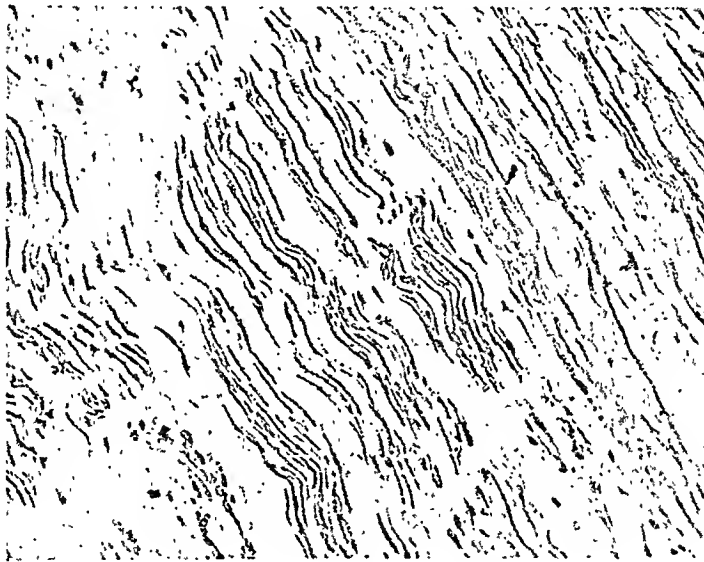


Fig. 6.—Case 5. (A) Ischemia of left tibial nerve (pale lower part) with good injection with dye (dark upper part) in vasa nervorum above level of thrombosis in posterior tibial artery and its neural branches.

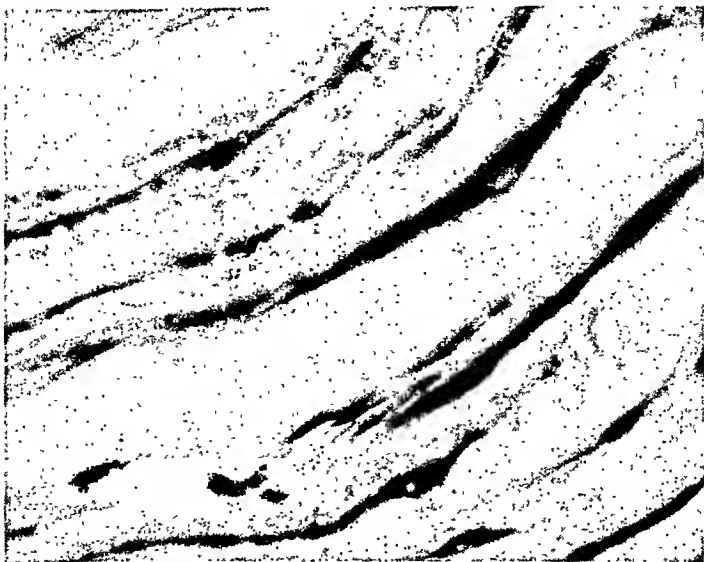
(B through F) Sections of ischemic portions of this nerve. Note: absence of dye, thickened walls of arterioles and capillaries, fibrosis, and patchy degeneration of nerve fibers. Hematoxylin—eosin.



D



E



F

Fig. 6—Cont'd.

(5) A middle-aged man with diabetes developed gangrene of the left first and second toes. He had anesthesia of the plantar surface of the foot and could not flex the toes. Mid-thigh amputation was required. The popliteal artery was injected with Chicago blue dye; dissection of the vessels and nerves was then carried out. A thrombus occluded the mid-portion of the sclerotic posterior tibial artery. The accompanying tibial nerve was well injected with dye above the level where the artery was occluded by the thrombus. Below this level the nerve (Fig. 6) was white and free of dye except for a small portion about 1.0 cm. in length supplied by a patent nutrient artery that apparently received its blood through collateral anastomoses from the lower middle part of the less severely sclerotic peroneal artery. The lower part of the anterior tibial artery was sclerotic but not occluded, and the peroneal nerves were quite well injected. The changes in function were due to ischemia of the lower tibial nerve. The small vessels were nearly or entirely occluded by proliferation or thrombosis, with loss of many axones and myelin sheaths (Fig. 6, *B* through *F*).

(6) An elderly woman with chronic rheumatic heart disease, atrial fibrillation, myocardial infarction, and thrombi in the left atrium and ventricle suddenly developed severe pain and pallor in the right foot and toes, followed by loss of pain and sensation over these areas. Gangrene of the dry type required supracondylar amputation. Several weeks later similar events affected the left foot, toes, and lower leg, with, in addition, loss of sensation of the lower leg and inability to flex or extend the left toes and ankle. When these two limbs were dissected after injection of the popliteal arteries, embolic and thrombotic occlusions of the sclerotic arteries were found at the level of the ankle in the right limb and about two inches below the knee in the left extremity. On the right side, the blood vessels of the nerves were well injected above the ankle but uninjected below that. On the left, the nerves were ischemic, as shown by injection, below the point of arterial occlusion in the upper third of the leg. The branches of the nerves going to the skin and muscles in the right leg arose above the thrombosis, while in the left leg the nerves to these structures came from below the level where the two branches of the sciatic nerve were devascularized by the thrombi. These findings explain the difference in neurological abnormalities of the two limbs; the ischemia of the nerves developed at different levels. Since the innervation of the flexors and extensors of the left toes and ankle was from devascularized nerves, power of movement of these parts was lost on the left but retained on the right side where the nerves were ischemic only below the origin of branches to the muscles moving the toes and foot.

(7) In other similar cases, injection of dye into the popliteal artery of amputated legs revealed poor injection of the blood supply of the nerves in portions supplied by thrombosed arteries or vessels obliterated by proliferative lesions. In two patients with extensive phlebothrombosis of the foot and leg, retrograde propagation of the thrombus had obliterated the blood supply of the peroneal and tibial nerves. These patients had shown loss of sensation over the foot and toes, with loss of ability to move the toes after an initial period of severe pain of the foot and calf.

(8) A young man with chronic thrombosis of the inferior vena cava developed extensive dilatation of collateral anastomoses for the return of blood to the heart. On post-mortem examination, the venous vasa nervorum of both sciatic arteries were found to be enormously dilated. Some of these vessels in the sciatic nerves had lumina 2.0 mm. in diameter. This finding shows that another role of the vasa nervorum can be to serve as potential collateral circulation for the relief of obstruction in other vessels. I have not yet found any cases where the arterial vasa nervorum adequately served this function as the venous blood vessels of the nerves did in this case. However, such an occurrence might be expected to happen occasionally, especially during embryonic or even early postnatal life. At these stages the arteria comitans nervi ischiadici approaches the obturator and femoral arteries in size, only to become insignificant in size with later growth.

(9) During a recent supracondylar amputation, it was noted that the femoropopliteal artery was closed by sclerosis and thrombosis so that it did not bleed when cut and that rather troublesome bleeding from the cut sciatic nerve occurred. In this instance the sciatic vasa nervorum were serving as partial, though insufficient, collaterals for the obstructed major artery. This 48-year-old woman, without diabetes, suddenly developed pain in the foot, but after two days had no pain, sensation, or power of motion in the foot, toes, and lower leg. The foot and toes became cold, black, and shrivelled, and the skin of the front and back of the leg developed large

vesicles. Dye injected into the amputated popliteal artery below its occlusion filled the vasa nervorum of the sciatic nerve and upper parts of its branches very well. At about the middle of the posterior tibial artery there was a firm, attached thrombus. The tibial nerve at this level appeared hemorrhagic, but below this level, was white and free of any dye. Other arteries and veins had partially occluding thrombi, and the other nerves were injected with dye only in irregular patchy areas. In some places, the thrombi in the vasa nervorum were plainly visible (Fig. 7). Many sections from this limb, as in the others already described, were stained with several methods (for example, Masson, Weil myelin, Bodian-silver impregnation, hematoxylin-eosin, Mahon myelin). Severe intimal proliferation, elastic fragmentation, eccentric atheromata, luminal reduction, thrombosis, extravasation of blood, moderate to marked demyelination, and necrosis of nerve fibers were seen in many sections at levels where dye was absent. In levels where the dye was well injected, these changes were missing or strikingly less. The arteriolar and capillary changes were seen in epineural, perineural, intrafascicular, and interfibrillar vessels. Perifascicular or perineural tissue was excessive in the ischemic areas. Even the vasa nervorum of the nerves in the walls of the thrombosed posterior tibial artery were thrombosed.

(10) Segmental ischemia of a sciatic nerve was seen during an exploratory operation for relief of extreme pain with paralysis of several months' duration in a young man with syphilis. This began a few minutes after a bismuth preparation was injected into or near the sciatic nerve instead of intramuscularly. During operation, dense fibrous adhesions constricted the nerve and obliterated its vasa nervorum. These adhesions were removed as carefully as possible. Pain was relieved and in time the paralysis improved partially. Syphilis probably played no role in this vasoneuropathy. Distinction between effects of ischemia and constriction of axones by the adhesions is difficult.

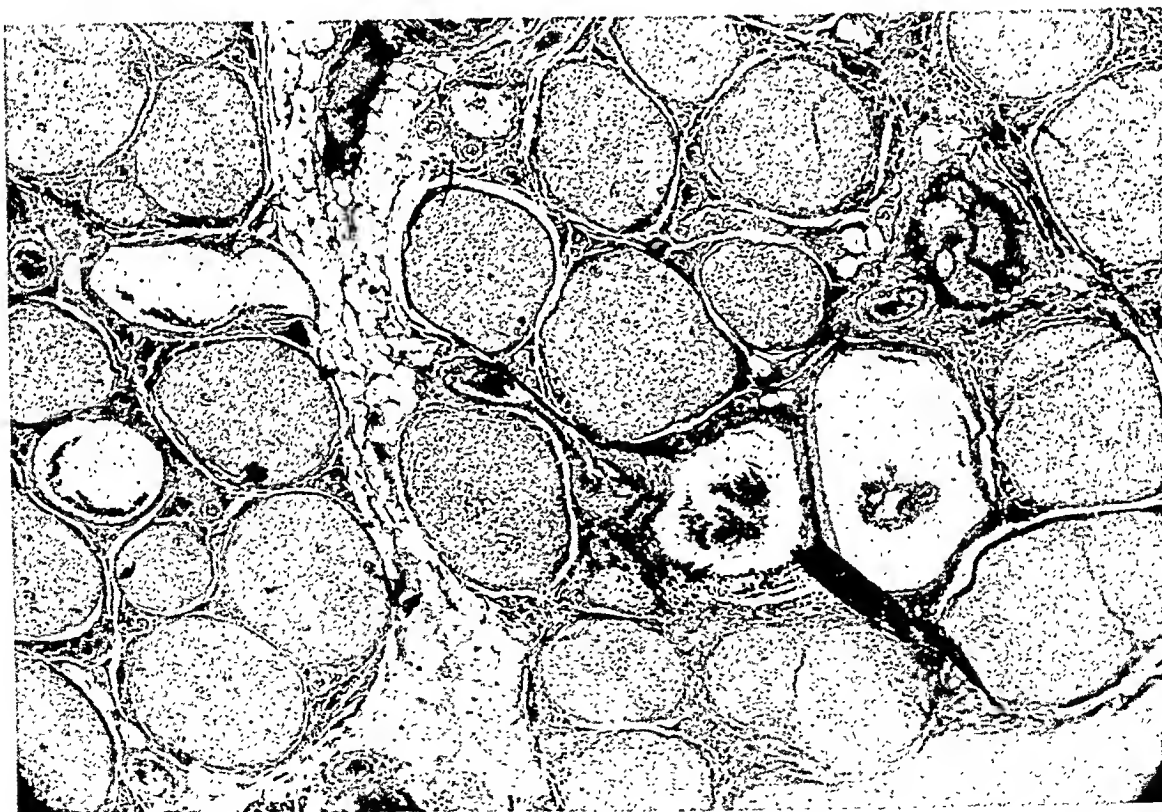
(11) Observations on myself consisted of noting the effects of compressing the radial, sciatic, sural, common peroneal, or plantar nerve against a firm surface, or by hyperabducting the arm, until the onset of tingling, numbness, pain, or weakness of muscles. When the compression was removed, normal sensation returned progressively over a period of one to three minutes in a steplike manner. With each pulse beat, the symptoms improved a little more until normal sensation and motion were possible. This suggests that the symptoms were due to ischemia from obliterating the vasa nervorum. If the axones had been injured, the restoration to normal would be expected to take a much longer time and not to have the phasic improvement related to each pulse.

LITERATURE

The literature on the blood supply of the nerves has been thoroughly reviewed in recent years by Adams,⁵ Sunderland,⁶⁻⁸ and Fetterman, Spitler, and Roberts¹; therefore repetition of this is not necessary. Isenflamm and Doerffler⁹ in 1768 seem to have been the first to ascribe importance to the vasa nervorum in the causation of various peripheral nervous disorders. Most of the reports have dealt with the anatomic distribution of blood vessels in various specific nerves or with hypothetical discussions of the possible role of the blood supply of the nerve in accounting for the symptoms in patients with vascular diseases. Relatively little actual experimental work on the subject has been found reported in the literature. In 1905 Okada¹⁰ described degeneration of the sciatic nerve in rabbits after ligating the inferior gluteal artery. Koch,¹¹ also working with rabbits, observed that a blood supply is necessary for a normal current of injury in the nerve. Adams⁵ in 1943 repeated the experiments of Okada but found that ligation of the inferior gluteal artery did not result constantly in degeneration of the sciatic nerve unless manipulation with possible injury of the nerve also occurred. Bentley and Schlapp¹² obliterated the blood supply of nerves by pressure with mercury-filled bags and found that the ability of the nerve to con-



A



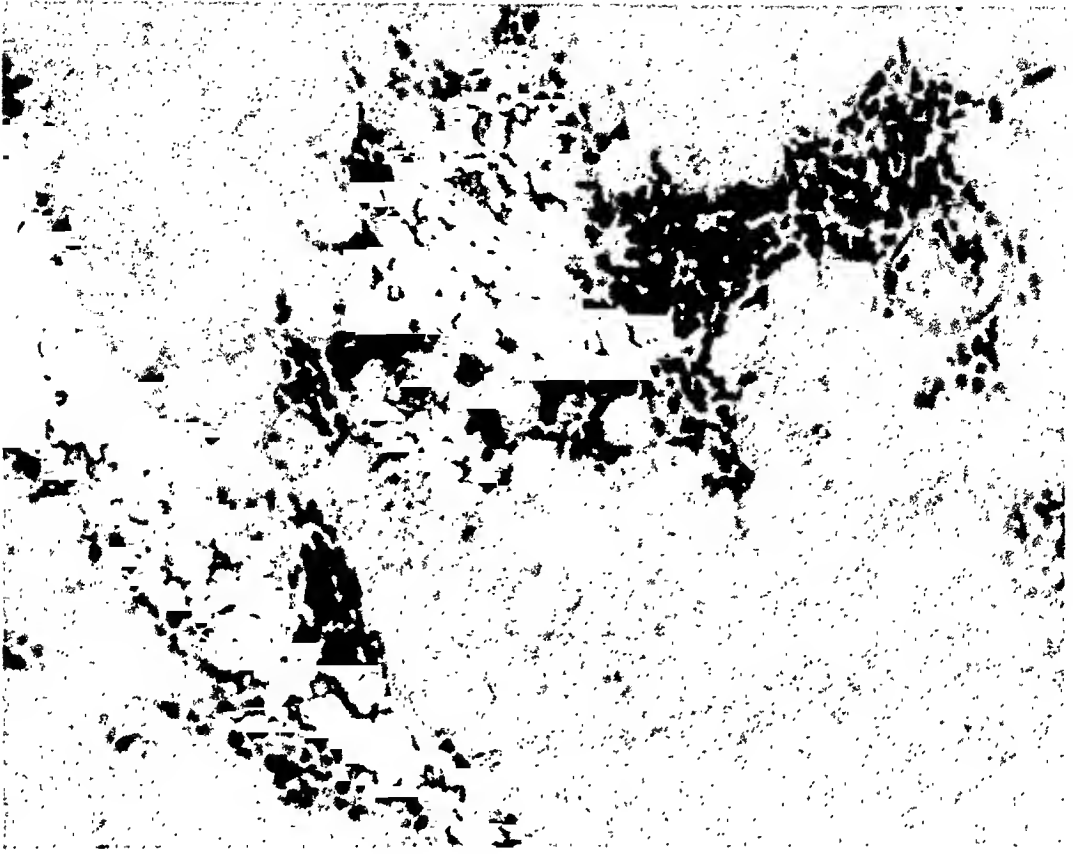
B

Fig. 7.—Case 9. (A) Dissection of nerves and vessels of left leg, after injection of dye in popliteal artery. Contrast well-injected sciatic and upper tibial nerve with ischemia of lower tibial nerve below thrombosis of posterior tibial arteries and its neural branches. Ischemia of superficial peroneal nerve also, below thrombosis of dorsalis pedis artery.

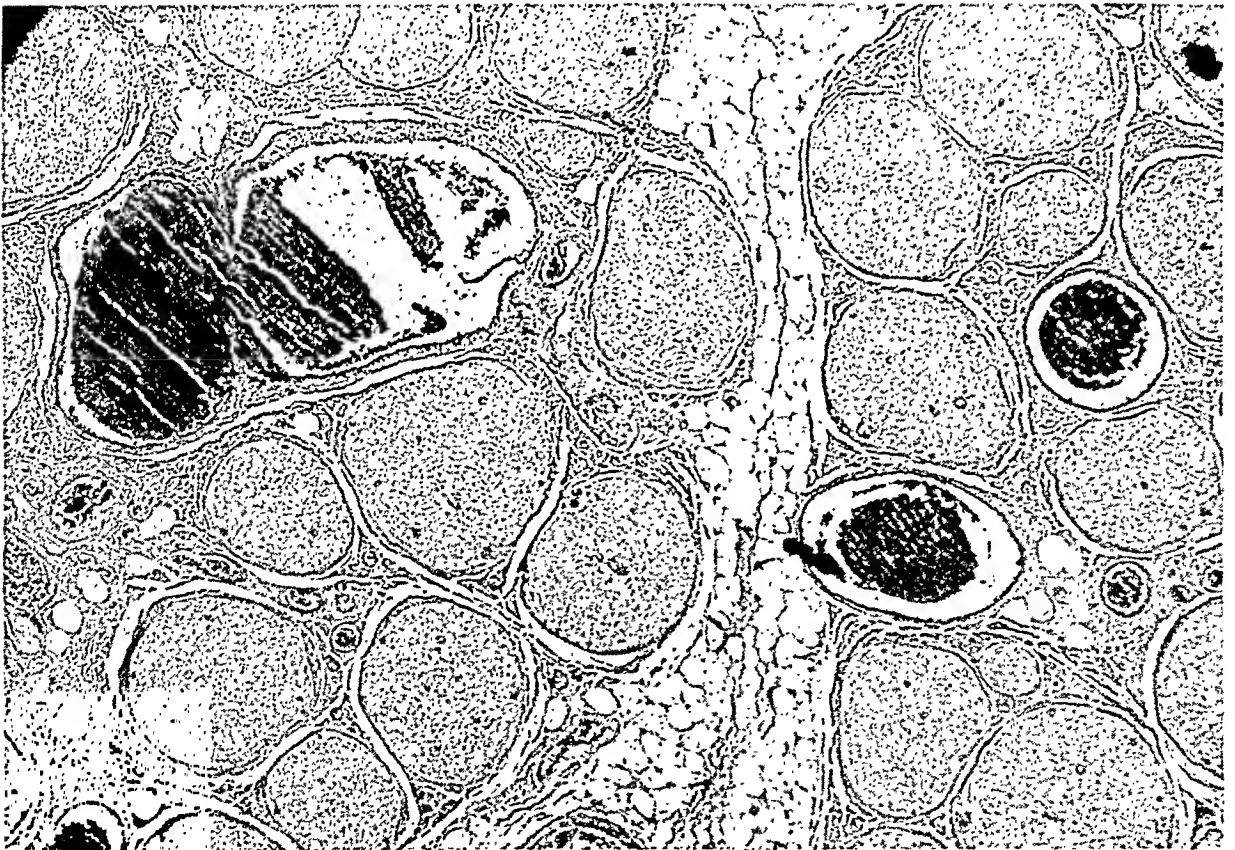
(B) Section of isehemic portions of tibial nerve. Myelin and Masson stain.

(C) Section of isehemic portion of tibial nerve, with extravasation of blood from occluded vasa nervorum, and surrounding this, areas of degenerating axone cylinder and myelin sheaths. Weil myelin stain.

(D) Dilated vasa nervorum in sciatic nerve at level of amputation, above injection.



C



D

Fig. 7—Cont'd.

duct impulses was impaired by a pressure which was thought to be adequate for occluding the vasa nervorum without injury to the nerve itself. Denny-Brown and Brenner¹³ believed that the lateral peroneal nerve was more susceptible to injury by being pressed against the fibula, because this nerve suffered more from ischemia produced by a tourniquet than did the medial peroneal nerve.

The effect of local ischemia upon human nerve fibers in vivo has been studied by Thompson and Kimball¹⁴ and very recently (since my work was done) by Kugelberg.¹⁵ In both studies ischemia was produced by a compressing sphygmomanometer arm band. Thompson and Kimball reported that the threshold for sensation to electrical stimulation fell rapidly and progressively for the first twelve minutes of ischemia and then sharply rose. This indicates that ischemia of a nerve first increases and later diminishes the irritability of the nerve. Kugelberg, with the aid of electromyography, found that a local area of ischemia produced two forms of spontaneous activity: (1) that occurring during ischemia and consisting of isolated action potentials of irregular frequency; and (2) that seen after ischemia and consisting of repetitive discharges which occurred in bursts. When the nerve fiber ceased discharging, though the excitability was still high, a passing action potential discharged a burst of spikes and acted as a "trigger" of a trigger zone. This mechanism was easily fatigued. Both studies seemed to confirm the opinion of Lewis and associates¹⁶ that such ischemia affects the nerve endings. These papers review the difficulties in distinguishing between the effects of compression and anoxemia of nerve fibers and especially cite the work of Bishop and associates¹⁷ and of Gasser.¹⁸ Wright¹⁹ and De Takats²⁰ have recently renewed the interest in ischemic peripheral neuropathy.

I have found no reports of experimental interference with the blood supply of nerves in which injury to the nerve itself or to other tissues was as carefully excluded as in the acute and chronic experiments which have been described. Likewise, in previous studies there has not been as careful integration of clinical observations and anatomic findings in human nerves as has been carried out in these studies.

Ischemic lesions of nerves, resembling those found in the cases of this study, have been described by Woltman and Wilder,²¹ Barker,²² and by Priestly²³ in studies on patients with diabetes mellitus, thromboangiitis obliterans, and arteriosclerosis. These authors noted proliferative lesions in the vasa nervorum, especially those in the thickened perifascicular fibrous tissue, patchy necrosis of nerve fiber bundles, and various combinations of wallerian degeneration, fibrosis, edema, atrophy, lymphocytic infiltration, inflammation, and thrombosis of the vasa nervorum. The use of injection methods in their studies would have been of great value. Karnosh²⁴ has attributed sciatic causalgia to ischemia of the sciatic nerve. Fetterman and Spitler¹ discussed cases of trauma, embolism, arteriosclerosis, diabetes mellitus, Buerger's disease, periarteritis nodosa, syphilis, and polycythemia vera as examples of peripheral neuropathy attributable to ischemic vascular disease of nerves. Many other writers have mentioned in varying detail the concept of neuropathy due to a defective blood supply in various regions of the body, including the ear, eye, trigeminal ganglion, and extremities.

Vasoneuropathy is caused by frostbite, immersion, and trench foot, and possibly by burns. Thrombosed vasa nervorum are present in such states and may contribute to the clinical findings. There is lack of agreement on whether neural ischemia is cause or effect of other pathologic changes in frostbite and immersion foot, according to Friedman,²⁵ Denny-Brown and associates,²⁶ and Ungley and Blackwood.²⁷

These papers are of great value, when considered in the light of the work reported here, in clarifying the mechanism of the findings and complaints in cases of causalgia, phantom limb, and thermal changes on the basis of occlusive or vasospastic neuropathy.

DISCUSSION

In the acute experiments described in this paper, it was shown that the blood supply of a nerve is very abundant and that this blood supply may be obliterated in a variety of ways which are analogous to the effects produced clinically by injury or disease in human beings. When the blood supply of a nerve was obliterated by ligating a single nutrient artery or the nutrient arteries of a small segment, only a partial or patchy ischemia usually occurred because collateral anastomoses through the longitudinal vessels in the nerve could maintain adequate nutrition. This belief that the longitudinal vessels have considerable importance in maintaining the function and structure of the nerve was corroborated by the survival experiments where ligation of segmental nutrient arteries only was carried out. This was in keeping with the clinical observation that single or several nutrient arteries may be ligated or obliterated without constant permanent injury to the function of a nerve during surgical procedures where a nerve is exposed, repaired, or transplanted. If the epineurium was stripped, with removal of the important longitudinal epineural plexus, the nerve was more ischemic in the stripped segment than in the normal nerve. In both the acute experiments and in the survival experiments of this type, there was more commonly evidence of disturbed function than in the group with ligation of single nutrient arteries. In such cases, nourishment of the nerve could occur only through the small vessels within the central part of the nerve and this relatively poor blood supply could make the nerve more susceptible to ischemia or injury from any other cause.

That stretching of a nerve could produce obliteration of the blood vessels in the nerve was clearly shown in the acute experiments performed in this study. Moreover, these results are of value in explaining the frequency with which nerve function is lost when nerves are stretched excessively during surgical procedures, by dislocations and faulty position, or by expanding tumors. This study shows that obliteration of the vasa nervorum by stretching of a nerve frequently occurs in man and is responsible for such clinical symptoms and findings as pain, numbness, tingling, paresthesia, weakness, paralysis, atrophy, hyper-reflexia, and other disturbance in the extremities. Such stretching can occur during prolonged unusual positions such as sitting with the legs crossed, keeping the arms elevated above the head or sleeping in an unusual position.

Closely related to this mechanism is closure of the vasa nervorum by compression of the nerve which may result from similar instances of unusual posture, (for example, pressure on the sciatic nerve by sitting on the edge of a chair, pressure upon a nerve during examination, sleep, or operation, and pressure by bandages, tourniquets, casts, or constricting types of clothing). The neurovascular syndrome, recently reviewed by Wright,¹⁹ is probably due to ischemia of nerves caused by pressure on or stretching of the vasa nervorum. We have seen recently three patients with chronic tingling or pain in the hands and arms, especially along the ulnar side, after first awakening. In each case the radial pulse became obliterated at some point of extending, rotating, and abducting the shoulder. The symptoms were relieved by changing the customary habits of sleeping on the arm. As in Wright's cases, this favors the neurovascular explanation of the complaints.

The acute and survival experiments with injection of embolic material into the nutrient arteries establish the fact that removal of blood supply to a segment of a nerve without injury to the nerve itself may result in impaired function and structure of the nerve. In these experiments the small blood vessels throughout the nerve were occluded without compressing or stretching the axones and without allowing the opportunity for nourishment to occur by way of collateral anastomoses with longitudinal vessels or other segmental arteries. Such experiments have their homologue in human cases where embolism, thrombosis, or proliferative lesions in the vasa nervorum or in their source of blood supply result in ischemia of a peripheral nerve. On the basis of the acute experiments showing that air injected into nutrient arteries caused a patchy type of injection with dye, it is believed that aeroembolism can cause dysfunction of the peripheral nerves by partial obliteration of their vasa nervorum. In patients suffering from high altitude or decompression sickness, symptoms and signs indicate early involvement of peripheral nerves in many parts of the body (for example, nerves of the ears, eyes, muscles, and about the joints) which may be explained best as being due to partial ischemia of these nerves by aeroembolism.

Although the experiments and clinical investigations described in this presentation involved only the larger nerves of the extremities, I believe that the role of the blood vessels in every nerve of the body may be equally as important. On the basis of this reasoning, it is possible to explain many common or bizarre symptoms affecting localized areas, such as the ear or eye, or widely scattered areas throughout the body, as in a condition where ischemia of many widely scattered nerves could exist. Embolism from vegetations, mural thrombi or plaques in the aorta, gas bubbles, bacterial clumps, tumor cells, or fat particles may be distributed by the blood stream to the vasa nervorum in any organ or part of the body and so affect the nerve supply in that organ. Increased viscosity of the blood, resulting from dehydration, polycythemia, hyperglycemia, or other causes, and slowing of blood flow predisposes to thrombosis, and this can occur in the small blood vessels of nerves as well as in large vessels. Small nerves have their individual blood supply as well as large nerves, as can be seen in sections of injected material or by using a transparent chamber grafted into the skin of the rat's back.

There is little available knowledge regarding the role of the blood vessels in nerves of the sympathetic system. An analogy with the experiments (described here) on the somatic peripheral nerves suggests the belief that some dysfunctions of the viscera may be due, at least in part, to similar lesions affecting the vasa nervorum of the sympathetic nerves. Recently De Takats²⁰ has discussed this problem briefly in a report on 'proliferative arteriolar changes in the dorsal root ganglions of diabetic patients. The lymphatic vessels of nerves may also have an important role, but no studies of this are known.

On the basis of these experiments and observations on patients, it seems likely that acute occlusion of vasa nervorum may be accompanied at first by severe pain, paresthesia, or hypersensitivity, and may be followed later by disappearance of these abnormalities with possible anesthesia or paralysis. This may be due to hyperconductility of the axones during the early or incomplete stage of ischemia, with loss of pain and sensation resulting later when the nerve has lost its ability to conduct any impulse as a result of complete or protracted ischemia. Thus, the pain of intestinal cramps may be due to ischemia of the nerves in the intestinal wall caused by spasm or distention. If distention or spasm is prolonged, pain is apt to disappear because the ischemic nerve has lost its conductivity. Or, the pain of angina pectoris may be great during the earlier stages when ischemia of cardiac nerves is only partial, but often disappears after myocardial infarction occurs and occlusion of a coronary artery removes all blood supply to these nerves. My hypothesis for explaining the infrequency of typical cardiac pain in patients with hypertrophied hearts has been presented previously.⁴ According to that study, the myocardial nerve fibers remain close to their capillary blood supply and so do not suffer ischemia proportional to that of the muscle fibers in cardiac hypertrophy. The muscle fibers enlarge with hypertrophy and push the capillaries, which do not multiply, farther apart than in the normal sized heart. Therefore, the muscle fibers are poorly nourished and function poorly, but the nerve fibers remained well supplied with blood and do not give rise to the painful sensations arising from ischemic nerves.

"Referred pain" is still poorly understood. Using the findings of this study, a reasonable hypothesis may be constructed to explain referred pain on the basis of ischemia of a peripheral nerve to skin or muscle. Such a nerve may become ischemic as a result of spasm of its vasa nervorum and cause painful sensations in its area of distribution. Such spasm may be induced by stimuli coming from the autonomic cell body groups in the central nervous system segment where the afferent nerve fibers from the injured visceral organ terminate. For example, "cardiac pain" in angina pectoris or myocardial infarction may be referred to the skin and muscle of the sternal, pectoral, or left arm regions, because the nerves to those areas become ischemic due to a reflex arc composed of the following components: (1) anoxia of a myocardial nerve stimulates (2) impulses along afferent cardiac nerves to (3) dorsal root ganglion cell bodies in the cervical segments and their central axones, terminating on (4) cell bodies in the dorsal part of the lateral horn of gray substance (the dorsolateral or intermediolateral groups of cells), which in turn, send (5) efferent sympathetic effector

axones via the white rami communicantes to the smooth muscle in the vasa nervorum of peripheral nerves distributed to the areas of "cardiac pain"; (6) spasm of these vasa nervorum produces ischemia of the nerve which causes impulses to go over the spinothalamic tracts from these peripheral nerves and results in consciousness of pain in the area supplied by these ischemic nerves (Fig. 8).

SCHEME SHOWING CIRCUIT FOR REFERRED CARDIAC PAIN ON BASIS OF SPASTIC VASO-NEUROPATHY

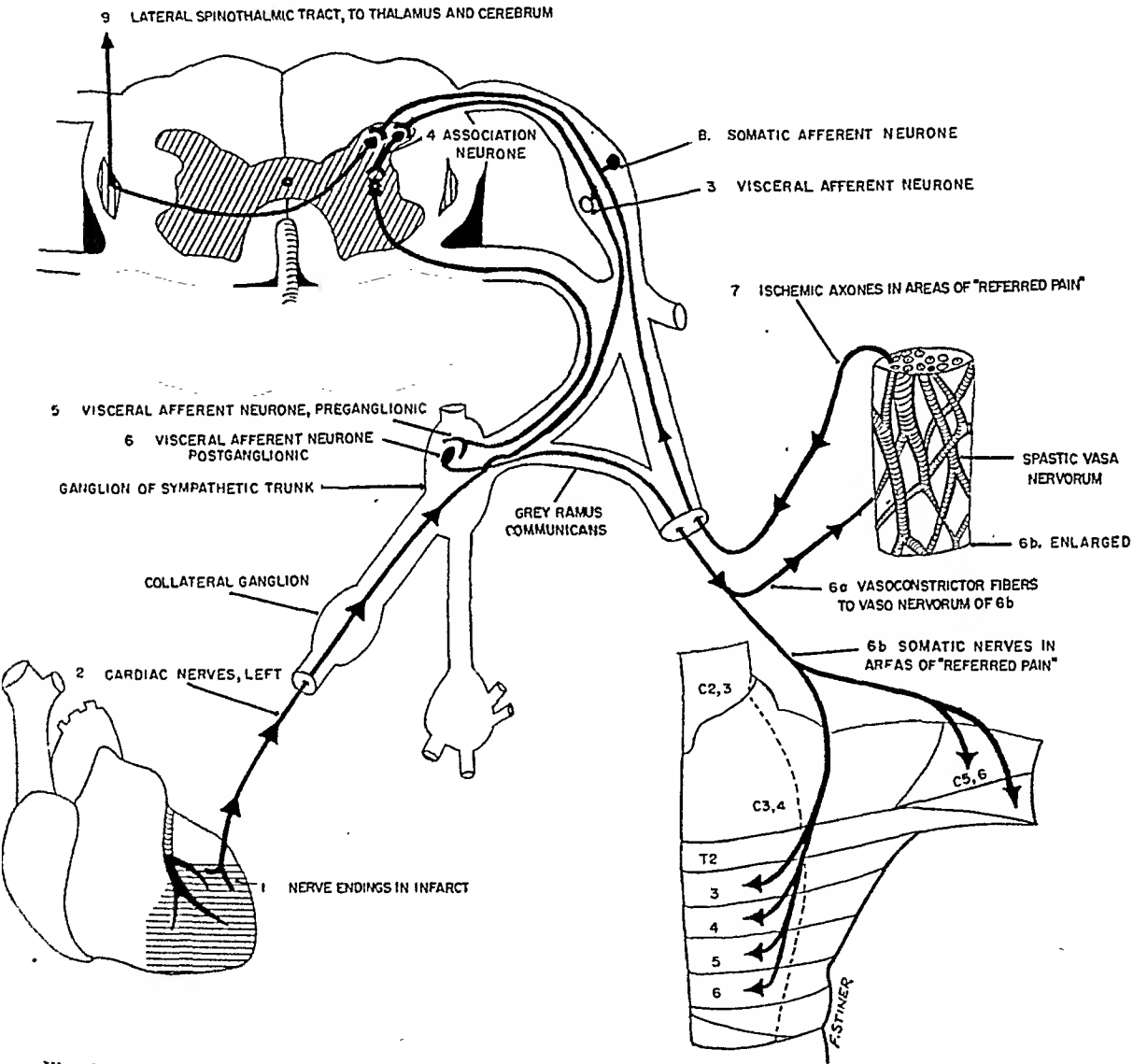


Fig. 8.—Reflex arc for "referred pain" on basis of vasospasm of vasa nervorum in peripheral nerves.

Information of therapeutic value to be derived from these studies is indirect. There is emphatic support of the need for careful manipulation of nerves during surgery with every effort being made to avoid (1) obstructing the blood

supply to nerves, (2) stripping of the epineurium, and (3) stretching or compressing nerves in any way. Inasmuch as ischemia of the nerve can result in its disintegration, efforts to prevent this may indicate at times the use of sympathetic nerve block and vasodilating or anticoagulant drugs.

It is probable that ischemia can prevent or hinder the regeneration of a nerve following injury by trauma, infection, or other cause. Experiments have been started to evaluate the role of the vasa nervorum in the regeneration of severed nerves. Likewise, the value of vasodilating drugs, anticoagulants, nutritional therapy, or sympathetic block needs to be evaluated as far as their effect upon the vasa nervorum is concerned. Initiation of thrombotic, spastic, and proliferative vascular lesions can be tried by injecting ferric chloride, hyper-renin, or sodium morrhuate into the nutrient arteries of nerves.

The role, if any, of the vasa nervorum in many other disorders should be investigated. These disorders include hypertension, cardiac arrhythmias, varicose veins, nutritional deficiencies, pernicious anemia, diabetes mellitus, and referred pain. Patients with any of these conditions which decrease circulatory efficiency need to be cautioned against lowering the threshold for ischemia in any way. They must be taught to avoid crossing their legs, sitting improperly, sleeping on their arms or with the limbs compressed and angulated in any way, or wearing any constricting clothing or dressings. Tobacco should be avoided, especially by patients with neuropathy of any type, because the superimposed vasospasm may make the neural ischemia complete and irreversible.

CONCLUSIONS

1. The blood supply of nerves has been shown to be very abundant. The smallest nerve has an adequate blood supply.
2. This blood supply was obliterated by ligating nutrient arteries of a nerve, by stripping off the epineurium, by compressing a nerve or stretching it, and by injecting embolic substances into a nutrient artery. Having produced ischemia of the nerve by these methods, it was studied by injecting dye through the aorta into the vasa nervorum, and was found to alter the function and structure of the nerve.
3. Peripheral nerves of man may be made ischemic by similar processes and by proliferative, vasospastic, or thromboembolic vascular diseases affecting either arterial or venous blood supply of the nerves in a great variety of clinical conditions (for example, diabetes mellitus, thromboangiitis obliterans, arteriosclerosis, arterial embolism and thrombosis, phlebothrombosis, stretching or compression of nerves, anemia, or hemoconcentration). Sensory and motor changes were closely correlated with ischemia of nerves in the cases studied by injecting dye or by sections.
4. Crossing the legs, sleeping or sitting in a position that causes compression or stretching of nerves, and the use of constricting clothing or vasospastic drugs like tobacco should be avoided by patients with ischemia of limbs. Tingling, numbness, and similar mild complaints may indicate early stages of ischemic

neuropathy and may, therefore, be signs of serious import. Benefit may follow vasodilatation and correction of causal factors.

5. A "reflex arc" for explaining "referred pain" on the basis of neural ischemia is proposed.

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EXPERIENCE WITH THREE VASCULAR FRAGILITY TESTS IN HYPERTENSION

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FOR many years clinicians have noted hemorrhagic tendencies in a certain percentage of their hypertensive patients. Although abnormal vascular fragility represents a clinical condition of obscure and multiple etiology, new interest has been aroused in the field by the introduction of new agents reported to have possible favorable effects in abnormal capillary fragility.¹⁻⁴ Most investigators have used one of several different tests to determine abnormal fragility, all based on the number of hemorrhages counted in a specific area following the application of suction or a constricting band.

METHODS

A number of methods have been devised for measuring capillary fragility. These may rightly be divided under two major headings:

1. The negative pressure method, developed by Hecht,⁵ da Silva-Mello,⁶ Dalldorf,⁷ and others.
2. The positive pressure method, based on the work of Leede,⁸ Göthlin,⁹ Beaser and associates,¹⁰ and others.

The negative pressure method measures the frequency of capillary rupture or diathesis at graded levels of negative pressure over a selected time period. The end point or critical pressure varies according to the criteria selected.

The positive pressure method consists of the application of a constricting band, such as a blood pressure cuff, at a definite pressure, and counting the number of petechiae occurring during a given time period.

The results of one investigator are difficult to compare with those of another because of variations in criteria, technique, and interpretation of results.

In this particular study, we have tried to compare three different methods which were used simultaneously:

1. The Göthlin Test,⁹ a positive pressure method in which a blood pressure cuff is inflated to 35 mm. Hg for fifteen minutes, and to 50 mm. Hg for fifteen additional minutes. The number of petechiae is counted in a 6 mm. circle in the antecubital fossa.

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2. The negative pressure test, using an apparatus designed by Dr. Carl Johnson.¹² A suction cup 1.0 cm. in diameter is placed on the ante-cubital fossa for thirty seconds, and moved to a contiguous area for each reading. The number of petechiae is counted at pressure levels ranging from 100 to 700 mm. Hg, rather than selecting the appearance of 1 to 3 petechiae as the end point (see Chart 1).
3. A cuff trauma test of our own, in which a blood pressure cuff is inflated three successive times from 0 to 300 mm. Hg and allowed to return to 0 slowly, as in taking a blood pressure. The area under the cuff and distal to the cuff is observed for petechiae and the frequency graded 1 to 4. Grade 1 represents a few petechiae under the cuff; Grade 4 a mass of petechiae down the forearm and onto the dorsum of the hand.

NEGATIVE PRESSURE CAPILLARY FRAGILITY TESTS

in
Hypertensive and "Normal" Control Patients
(shows similarity in type of distribution)

• Each dot represents 1 patient

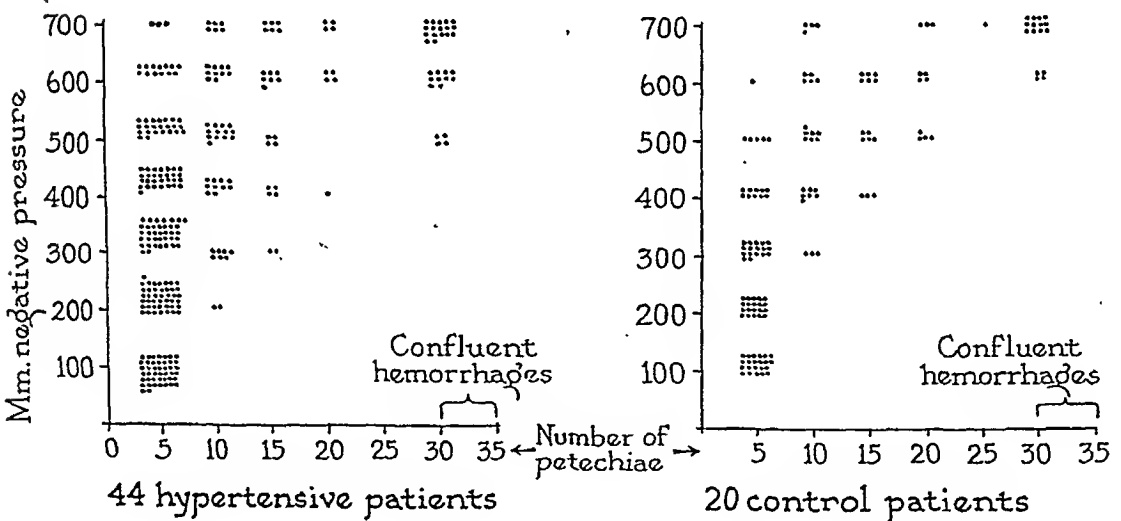


Chart 1.

We have classified the patient as having increased capillary fragility:

1. If more than six petechiae are present after the first step of the Göthlin Test.
2. If a total of thirty or more petechiae are present at successive 100 mm. readings between 100 and 500 mm. Hg of negative pressure.
3. If a shower of petechiae are found under the cuff or distal to the cuff following inflation to 300 mm. Hg three successive times.

Our interest in rupture of the vessels of the skin and subcutaneous tissues dates back to the days when venesection was commonly employed in patients with hypertension who had suffered a cerebral vascular accident or left ventricular

heart failure. The occasional patient would show a shower of coalescing masses of petechiae in the extremity from which the blood was taken. A more prolonged application of the constrictor during the procedure occasionally resulted in massive areas of petechiae, which instantly became ecchymotic and disfigured the arm for ten to twenty days. It was our impression at that time that the appearance of such degrees of petechiae meant severe vascular disease in these hypertensive patients.

During the past twenty years of special interest in vascular disease, the periodic appearance of numerous hemorrhages under and below the blood pressure cuff of the hypertensive patient has been recorded. This phenomena of the rupture of the small vessels of the arm during the course of taking a blood pressure appeared often enough to cause us to standardize our technique, and for want of a better name, we have called it the "cuff test." After taking the blood pressure in a routine manner three separate times in order to establish the patient's basal level, we inflate the cuff until the column of mercury rises to 300 mm. three times, deflating the cuff completely and flexing the arm each time, after which the presence or absence of petechiae are noted. All members of our hypertensive clinic, as well as medical students, have learned to observe and grade the presence or absence of petechiae following this simple procedure. If no petechiae appear, the cuff test is reported as zero. If petechiae appear under the cuff but along the wrinkles only, it is considered Grade 1. If petechiae appear within other areas under the cuff, but not below the cuff, it is Grade 2. Petechiae appearing both under the cuff and under the antecubital fossa are Grade 3, and Grade 4 is recorded when the petechiae appear down the forearm or onto the dorsum of the hand.

These observations have demonstrated that: (1) The cuff test is usually negative in patients with hypertension. (2) Patients with a positive cuff test show wide variations in the degree of fragility from month to month, regardless of treatment. (3) Positive cuff tests were most often related to the severity of the disease, especially when the diastolic blood pressure is high. (4) The appearance of petechiae coincided with vascular crisis of hypertensive encephalopathy, retinopathy, nephropathy, or other vascular episodes. Such observations over several years have caused us to look upon the presence of a positive cuff test as a finding of real clinical interest, if not a warning of impending danger when it is Grade 3 or more.

However, many unexplained factors seem to cloud our interpretation. For instance, the tests seemed to be much more frequently positive in women. Second, a positive cuff test might occur in patients who had no hypertension or other evidence of systemic vascular disease. Third, patients with advanced nephritis and complicating hemorrhagic phenomena, such as vascular bleeding in the eye grounds, gastrointestinal, and respiratory tracts, or deep ecchymotic areas in the subcutaneous tissue, would often have a negative cuff test.

Recently, our interest has again been aroused by the introduction of new agents reported to have a favorable effect on hemorrhagic tendencies by increasing capillary resistance so that we have again given critical evaluation to a group

of hypertensive patients, both from a standpoint of methods of measuring increased capillary fragility and the effect of these newer agents on this fragility.

MATERIAL

We have studied a group of forty-four unselected new patients with hypertension as they entered the renal vascular clinic of the Northwestern Medical School. These patients comprise a random sample with a similar socioeconomic background without regard to disease severity or any other specific factor except that they had hypertension. Fragility tests were repeated once or twice weekly on all patients showing any evidence of increased vascular fragility, while those showing no abnormality and severity controls were tested once or twice each month.

Before presenting the results of our studies of capillary fragility in patients with hypertension, the following information is offered in so far as it affects the evaluation of any study of capillary fragility. Reported studies in twenty "normal" controls aided us in selecting what we considered to be the most suitable criteria and pitfalls involved in correctly interpreting our data.

1. The reliability of the Göthlin Test is in the variety of 0.90 (maximum 1.0) when negative tests alone are considered. As the test becomes progressively more positive, the reliability diminishes to .05 or below, when the number of petechiae range above 12 to 15.

2. Skin temperature has a pronounced effect on capillary fragility. Heat applied for two or three minutes to the forearm markedly increases capillary fragility. Likewise, fragility will decrease following the application of cold to the same area.

3. When positive or negative pressures are used as a measure of fragility, it is to be remembered that the weakest capillaries are being ruptured and tests which measure only a small portion of a large capillary population are subject to wide variations and follow a different type of distribution.

4. Skin thickness: Blondes, who are more likely to be thin-skinned, have a greater tendency to increased fragility than brunettes. Similarly, hirsutism strengthens capillary tone.

5. Other factors, such as tissue anoxia and the nutritional state of the individual, particularly as it applies to avitaminosis, complicate the interpretation of the test.

6. Endocrine factors definitely influence the susceptibility to capillary rupture. Brewer¹³ has shown that this susceptibility is greater premenstrually than at any other period during the menstrual cycle. He also demonstrated that adrenalin produces the same tendency in man. It is possible that both adrenalin and the adrenocortical hormone influence the ease of capillary rupture.

It is well known that women in menopause have a tendency toward formation of spontaneous ecchymotic-type hemorrhages. We have found that this is often associated with a positive cuff test and a marked increase in the Göthlin

index, even though there is no other evidence of vascular disease. Both the ecchymotic tendency and the capillary fragility will become more normal following adequate estrogenic substitution therapy, but are not affected by rutin or Vitamin C. This is well illustrated by the following case:

CASE 1.—Miss L. B., 45 years of age, came to the clinic complaining of the usual menopausal symptoms; hot flashes, increasing irritability, insomnia, and diminution of menstrual flow. In addition, she complained of numerous bruises on her legs, thighs, and arms which were in no way related to trauma. When the blood pressure was taken in the routine manner, showers of petechiae appeared beneath the cuff and down the forearm to the dorsum of the hand (4 + cuff test). The blood pressure averaged 145/85. The Göthlin index was 60. There was no evidence of blood dyscrasia and the prothrombin and bleeding times were normal. Rutin, administered in daily doses of 180 to 200 units for six weeks, had no effect on either capillary fragility or ecchymosis. Vitamin C, calcium, and sedation were also of no avail. Thereafter, estrogenic therapy was started and within fourteen days all positive tests of her abnormal vascular fragility as well as the areas of ecchymosis had disappeared. There has been no recurrence during the past ten months, during which time she has received an estrogenic substance.

7. Leonard Keeler,¹⁴ the well-known criminologist, in a personal communication has stated that the blood pressure cuff on the polygraph causes showers of petechiae to occur in a large number of subjects regardless of age, economic status, or blood pressure, although he reports a preponderance of increased fragility in women subjects.

8. We have previously mentioned that patients with advanced renal disease who have evidence of spontaneous hemorrhages elsewhere in the body, have normal cuff tests and Göthlin indices. This same fact obtains in patients with cirrhosis of the liver. These patients who show spider nevi, dilated abdominal veins, and esophageal varices, and who have nutritional abnormalities of the skin and body tissues, should be expected to show marked increase in their capillary fragility as measured by the positive or negative pressure techniques. However, capillary fragility is more often than not normal in spite of the fact that there are often gross changes in the prothrombin time, blood protein, blood cholesterol, and vitamins C and K.

9. Four of twenty control patients (20 per cent), free from cardiovascular disease but selected from the same socioeconomic status, revealed abnormal fragility. We also noted that repeated tests of the hypertensive group shows fluctuations which would change the category of the patient from borderline to normal.

A critical review of the results obtained in the hypertensive group, the control group, and in our pilot experiments leads us to doubt that repeated simultaneous use of the three tests adequately fulfills the need for a quantitative test of increased fragility. Even though a more accurate test should be developed that would measure more precisely the fragility of superficial skin capillaries, we would still be unable to draw any conclusions concerning the status of the capillaries anywhere but in the superficial layers of the skin. Factors which control vascular bleeding in the subcutaneous tissues and in the organ systems themselves cannot be measured by this type of test. Bearing these limitations in mind, the following results were obtained in a series of forty-four unselected patients with hypertension.

RESULTS

	NUMBER	PER CENT
1 Hypertensive patients examined	44	
2 Patients with increased fragility, according to the Göthlin Test Index	7	15.9
3 Patients with 30 or more petechiae between 100-500 mm. of negative pressure	7	15.9
4 Patients showing petechiae following 300 mm. cuff trauma test	11	25
5 Patients treated with potassium thiocyanate	22	50
6 Thiocyanate treated patients manifesting increased fragility	3	13.6

It can be seen from this tabulation that the increase of capillary fragility occurs in approximately 16 per cent of the hypertensive patients, both as measured by the Göthlin index and the negative pressure techniques. Although the cuff test is a much more rapid technique for measuring capillary fragility, it is not as accurate a measurement as the other tests.

In our series, 25 per cent of the hypertensive patients showed abnormal fragility by the cuff test. Griffith¹⁵ reported an incidence of 21 per cent increased fragility in 1,219 hypertensive patients. Our figures are quite similar to his. However, we must not forget that a certain percentage of normal individuals free from cardiovascular disease may also show increased capillary fragility as measured by both positive and negative techniques. In our group of control patients, 20 per cent showed increased capillary fragility.

Several authors have made the statement that patients undergoing thiocyanate therapy are likely to have abnormal capillary fragility. Shanno¹⁶ stated that eleven of his series of twenty-four cases undergoing thiocyanate therapy revealed this tendency. Zfass¹⁷ mentioned a favorable response of two cyanate-treated patients when given rutin in conjunction with thiocyanate. Griffith and Lindauer¹⁸ have also alluded to the possibility that potassium thiocyanate may increase capillary fragility. The incidence of decreased capillary resistance of hypertensive patients on cyanate therapy was 13.6 per cent, which is approximately the same incidence as that of the hypertensive group.

Contrary to the opinion of other observers, we feel that a strongly positive cuff test or a high Göthlin index in the presence of a severe hypertension probably means advanced vascular damage, provided that the patient is not in the menopause. For many years we have noted that capillary fragility will improve as the blood pressure is reduced. We have also found that cyanate therapy with a subsequent drop in blood pressure improves vascular tone rather than increases capillary fragility. The following case illustrates the effect of cyanate therapy and a subsequent reduction of blood pressure in a patient with severe vascular disease and a marked increase in capillary fragility.

CASE 2.—Mrs. H. L., white, 47 years of age, stated that a blood pressure of 190 was first recorded when she was 29 years of age. Seven years before she came under our care, she had been told that her blood pressure was 285, at which time she suffered vertigo and fainting spells. Thiocyanate was administered for "several months" in 1944 without effect and a thoracolumbar sympathectomy was done in two stages in June, 1945. Within four months after the extensive sympathectomy, the blood pressure was well above the capacity of the usual mercury instrument which records only 310 millimeters. The diastolic pressure was regularly recorded at 160 to 170 millimeters.

We first saw Mrs. H. L. in April, 1946, when her blood pressure was 310+/160. The skin of the arm and forearm broke out with a mass of fine petechial hemorrhages which coalesced into large areas while the blood pressure was being taken a second time. Because of the severity of the vascular rupture, the cuff was changed to the opposite side where another attempt to record the systolic pressure failed (310+/170) but the diastolic pressure was obtained. Again the peculiar fragility resulted in masses of ecchymosis down the forearm onto the dorsum of the hand to the fingers. Potassium thiocyanate was started and the record on May 13, 1946, when the blood thiocyanate had reached 6 mg. per cent, shows that lines of traumatic petechiae were found under the sphygmomanometer cuff, but none appeared on the skin of the antecubital space or forearm; the blood pressure was recorded at 226/130, 260/130, and 266/130. On June 15, 1947, no traumatic or other evidence of increased vascular fragility could be demonstrated; the blood pressure was 240/120, 220/120, and 220/120, and the blood cyanate was 100 mg. per cent.

Although this patient's blood pressure was unusually high, the sharp degree of vascular fragility, as indicated by the cuff test, was returned to a normal state after six weeks of controlled thiocyanate therapy. This favorable response to thiocyanate therapy is usually noted by the third or fourth week and a complete disappearance of abnormal cutaneous vascular fragility may be expected in four to six weeks.

An analysis of the individual cases manifesting increased fragility revealed several interesting conditions. Six of the seven patients showed evidence of advanced degenerative retinal changes and moderate to severe renal impairment, as shown by the presence of abnormal elements in the urine and poor renal function tests. Two of these patients submitted to thoracolumbar sympathectomies. The renal biopsies which were taken at the time of operation showed a diffuse arteriosclerosis as well as arteriolosclerosis. Three patients in this group gave a history of abnormal bleeding. Other associated disease conditions were: cardiovascular accident in one case, coronary thrombosis, detached retina, and Kimmelstiel-Wilson's syndrome. Here again we see that given a patient with advanced hypertension, the presence of abnormal capillary fragility probably means a severe generalized vascular involvement.

Rutin was administered in daily doses of 180 to 200 mg. to all patients showing abnormal fragility. Three of the seven patients continued to show borderline increased fragility during the two-month period of observation. One patient showed a temporary improvement during the first month, with a return to abnormal fragility during the second month in spite of continued treatment. In three cases capillary fragility returned to normal. No significant reduction in blood pressure was found in any of these patients. No signs of toxicity were noted. No other subjective or objective changes could be attributed to the drug. There was no change in the progress of the disease.

Our results compare favorably with those reported to us by Taylor and Page¹⁹ of the Cleveland Clinic, who repeatedly performed the Rumpel-Leede test on forty patients with hypertensive vascular disease over a six-month period. Twenty-two of their patients were given 300 mg. of rutin daily. Eleven of these had a decreased number of petechiae during period of observation. The other eleven showed no improvement, and of this latter group, three had cerebral vascular accidents. One had a myocardial infarction while taking rutin. The remaining eighteen patients received no rutin. Fifty per cent of this group

likewise showed a definite improvement in capillary fragility while under observation for a six-month period without treatment. None of this group developed signs of acute vascular insufficiency. In an attempt to establish the value of estimates of capillary fragility among patients with hypertension, the Rumpel-Leede test was performed on several hundred normal persons and patients with various diseases. Acutely ill patients over 50 years of age often showed increased capillary fragility. This was particularly true of patients with a significant amount of arteriosclerosis and accompanying hypertension. The degree of capillary fragility varied from month to month in hypertensive or other patients. With the general improvement resulting from bed rest and recovery from heart failure, there were usually fewer petechiae produced by the test employed.

It was the opinion of the observers that in their hands rutin was of no benefit in the treatment of hypertension or its complications.

DISCUSSION

We do not believe that any of the three tests described adequately fulfills the need for an accurate quantitative method for determining increased capillary fragility and the response to therapy. They are all gross qualitative category tests, subject to spontaneous variation in the same patient from week to week. Many complex factors influence the susceptibility of capillaries to rupture, and these same factors render the interpretation of results more difficult.

In view of the lack of sensitivity of the capillary fragility tests, and the many factors influencing the determinations, one must be careful in interpreting the response to therapy in a group of individuals.

Although rutin has been efficacious in correcting abnormal capillary fragility in a large series of patients, our results in a small group have been disappointing. Glazko and associates²⁰ have recently described a fluorophotometric method of determining the blood levels and excretion of rutin and other members of the flavone group. A great deal of additional pharmacologic study must be done before we can assign to rutin a prominent role in the correction of a possible deficiency state.

The possibility that thiocyanates, of themselves, increase capillary fragility is a debatable point. Our results do not show that thiocyanates increase capillary fragility; in fact, the tendency to capillary rupture appears to decrease as the blood pressure is lowered by thiocyanates.

Abnormal capillary fragility seems to be associated with the presence of advanced, diffuse degenerative arteriosclerotic changes. Rutin does lessen the tendency to petechiae rupture in some cases, but the results in our small group series have been disappointing.

SUMMARY

The efficacy of three tests used in measuring capillary fragility in patients with hypertension has been reported. A cuff trauma test, although less accurate than either the Göthlin index or negative pressure test, is rapid, simple to perform, and gives an excellent preliminary estimation of the severity of the vascular dis-

ease of the hypertensive patient. In addition, it is a guide to the degree of clinical improvement of patients undergoing cyanate therapy. The Göthlin index, although showing less variability than the negative pressure test, is probably not as sensitive as the latter. In doing the negative pressure test according to the technique as first described by Johnson, we do not believe that individual readings of the negative pressure at which the first petechiae appear in a small localized area are reliable criteria. For this reason, we prefer to do serial counts at 100 mm. gradations, from 100 to 700 mm. Hg, and count the total number appearing between 100 and 500 mm. of mercury. The most consistent results were found by this method.

Of forty-four hypertensive patients examined by three capillary fragility tests, approximately 16 per cent had increased fragility as measured by the Göthlin index and negative pressure technique. Twenty-five per cent had increased fragility following the cuff trauma test. Only 13 per cent of the cyanate-treated patients manifested increased fragility, while 20 per cent of our normal control patients showed increased fragility.

Even though it is our clinical impression that patients with a severe degree of hypertension who manifest a marked increase in capillary fragility as measured by the Göthlin index or cuff trauma test have widespread vascular disease, we cannot interpret, on a scientific basis, the condition of the generalized vascular bed in the cerebral, cardiac, or renal systems on the basis of studies of superficial capillary fragility.

Multiple extrinsic causes of capillary fragility aside from vascular disease must be considered before any interpretation can be made. Normal individuals without hypertension or end artery disease may show abnormal capillary fragility as measured by these tests. Likewise, patients with advanced degrees of generalized vascular damage may have normal capillary fragility. The degree of capillary fragility in any one individual is not consistent but varies from month to month.

CONCLUSION

1. Three capillary fragility tests, the Göthlin Test, the negative pressure test, and the cuff trauma test, have been compared and evaluated.
2. It does not appear as though any one of these tests adequately fulfills the need for an accurate quantitative test.
3. Abnormal capillary fragility was found in 15.9 per cent of forty-four hypertensive patients.
4. Thiocyanates did not increase capillary fragility in this particular series.
5. Rutin, administered in 180 mg. doses daily, reduced the susceptibility to capillary hemorrhage in three patients. In three, the results were questionable.
6. Abnormal capillary fragility was associated with advanced diffuse degenerative arteriosclerosis in most of our cases.

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NIGHT CRAMPS IN HUMAN EXTREMITIES

A CLINICAL STUDY OF THE PHYSIOLOGIC ACTION OF QUININE AND PROSTIGMINE UPON THE SPONTANEOUS CONTRACTIONS OF RESTING MUSCLES

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IN OCTOBER, 1940, we reported the successful management of "night cramps" with quinine sulfate¹ and stated that further investigation relating to the mechanism of action was being pursued. Many additional patients were treated from that time until government regulations restricted the use of quinine for general use. Twenty patients of this new series were followed in the Vascular Disease Clinic of the Cincinnati General Hospital over a protracted period for the purpose of investigating both the site of action of the drug and the physiologic factors responsible for the onset of the cramps. Because of the preclusion of the general use of quinine during the last few years, this report dealing with the pharmacologic and physiologic implications of the study has been withheld until the present.

MATERIAL

In contrast to the first group, which was selected from patients already attending the Vascular Disease Clinic for other conditions, the patients used in this study were referred by other clinics specifically for the care of "night cramps." Concomitant disease entities were to be expected. Most of these were coincidental. Some definite correlation, however, was established with certain disease entities. Fifty per cent of these patients were referred to us by the Diabetic Clinic. Twenty-five per cent of the patients were being treated for varicose veins of the legs or gave a history of having had varicosities. Consistent with the association of cramps and varicosities in this last group was the finding of a history of peripheral venous thrombosis or thrombophlebitis in many of our private patients who had night cramps. The incidence of arterial disease in these patients was high, but special vascular studies on ten of them showed serious arterial deficiency in only four. Avitaminosis, as evidenced by paresthasias of the extremities, was common, particularly in the older patients. Vitamin B complex deficiencies are frequently a cause of night pain and numbness

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in the distal portion of the extremities. Proved cases of vitamin deficiencies referred to our clinic by error and relieved by vitamin therapy were excluded from this study. In those in whom night cramps and avitaminosis coexisted, the muscle cramps were relieved first by quinine before instituting vitamin therapy, or thiamine chloride and yeast were administered initially and continued while the quinine and placebo capsules were alternated. In no instance did vitamin therapy relieve the muscle cramps.

METHOD, DOSAGE, AND RESULTS

The reports of Wolf and Kennedy^{2a,b} regarding the antagonistic effect of quinine hydrochloride and prostigmine salts upon myotonia and myasthenia gravis prompted our original trial of quinine sulfate for the relief of night cramps. It seemed important, therefore, to recheck not only the beneficial effect of quinine salts but also the action of prostigmine upon patients susceptible to these night cramps. Quinine sulfate, 3 grains (0.2 Gm.), a placebo, and prostigmine bromide, 7.5 or 15.0 mg. were prepared in identical capsules. Patients were started with either the placebo or quinine sulfate originally; if the latter, the placebo was substituted as soon as relief of the night cramps was noted. Three grains of quinine sulfate were experimentally established as the initial therapeutic dose and administered after each meal. The morning dose was of little benefit, except to those experiencing muscle cramps while resting during the day. Three grains of quinine at bedtime were sufficient in some instances; two grains were insufficient for most patients. Faster acting quinine dihydrochloride was given some patients at bedtime where cramps appeared promptly upon retiring. Later, three grains of quinine sulfate after supper supplemented by a similar dose at bedtime proved equally beneficial. Relief was usually obtained on the first or second night. Often it was complete at once; sometimes milder or less frequent cramps persisted for some days after treatment was begun. Repeated alternations with placebo capsules over long periods were possible in many patients. Eventually, after a varying degree of quinine therapy, release of muscle cramps persisted without medication. Whether this was due to the interruption of some metabolic cycle by quinine or to the natural history of the condition could not be established. Night cramps are usually periodic regardless of treatment. Relief, however, was so prompt in all cases and pain recurred so often with placebo capsules that there could be no question as to the specific action of the drug in this condition.

In those patients who came to the clinic complaining of night cramps and who received prostigmine bromide before the quinine, no alteration in the frequency or intensity of the cramps was acknowledged by any of the patients. One patient who was able to precipitate spasm of the muscles of the leg by forcefully extending his foot for twenty-five seconds received two ampules of prostigmine methylsulfate (1:2000) without influencing the time of onset of the cramps or the ability to obtain relief from them by pressing his foot upon the floor. Tests were made every five minutes from twenty to forty-five minutes after subcutaneous injection of the prostigmine. In only two patients did prostigmine bromide

induce muscle cramps after they had been relieved by quinine. This may have been coincidental since quinine gave relief despite continued administration of prostigmine in these patients and since prostigmine alone, upon discontinuance of quinine sulfate, failed to precipitate spasm.

Other Effects of Prostigmine.—It is possible that larger doses of prostigmine might have increased the night cramps. The dosage used, however, was adequate to produce other physiologic effects of prostigmine, the most interesting of which was peripheral vasodilatation. Patients with peripheral arteriosclerosis, while reporting no change in muscle spasms at rest, volunteered the information that their extremity "no longer felt cold," or that "the heaviness" had left, or that "life was back" in a toe which had been numb. Spontaneous burning pains often were abated or were reduced in intensity. One patient in his late forties noted marked improvement in intermittent claudication. The other patients with intermittent claudication were older and obtained little or no relief of muscle cramps on exertion. Perlow^{3a,b} also reported that intermittent claudication in arteriosclerotic patients was most refractory to prostigmine therapy.

Another effect of prostigmine was its action on joints with hypertrophic arthritis. Patients called our attention to increased motion in an ankle joint which had been restricted for years, or reported increased mobility in knees or feet. Subsequently, we have used prostigmine in a selected group of patients who were suffering from osteoarthritis and we have noted improvement in many of them. Trommer and associates^{4a,b} recently reported thirteen patients with rheumatoid arthritis who showed marked and prompt relief after the use of prostigmine. Our series was restricted to patients with hypertrophic arthritis and we noted beneficial response with relief of pain and stiffness of the joints within twenty to thirty minutes of the subcutaneous injection of prostigmine methylsulfate. The action may be one of relaxation of periarticular tissues through vasodilatation similar to that produced by short wave diathermy treatments, rather than relief from spasm by the action of prostigmine within the spinal cord, as described by Kabat and Knapp.⁵

Reports of uncomplicated cases with night cramps were published in our preliminary report. This additional history is added to show the existence of concomitant disease as well as to evaluate the action of prostigmine.

B. F., a Negro woman 60 years of age, came to the Vascular Disease Clinic on May 1, 1941, complaining of "night cramps." Her sleep had been disturbed for months by spasms in the calf muscles of the legs. The spasms were more pronounced following unusual activity during the day. In addition, she gave a history of adequately treated syphilis, diabetes mellitus which was controlled by dietary management alone, and arteriosclerotic heart disease in a state of compensation with digitalis therapy.

Physical examination revealed an alert woman who appeared much older than 60 years. In addition to generalized arteriosclerosis and hypertrophic arthritis, she had a smooth beefy-red tongue and complained that her feet "burned." Oscillometric tracings showed diminished pulsation in both legs. It was decided to postpone treatment for the vitamin deficiency until after the night cramps had been relieved.

Quinine sulfate, 3 grains, was prescribed after dinner and at bedtime. Two weeks later, she reported complete relief of the night cramps. This relief started on the day after quinine was

first given. Quinine sulfate was continued and, to combat the vitamin deficiency, thiamine chloride, 15 mg. together with an ounce of dried brewer's yeast, was given daily.

During the next six weeks there was much improvement in the vitamin deficiency. The dose of thiamine and yeast was thereafter kept constant and quinine sulfate therapy alternated with a placebo and prostigmine. On July 28, she reported severe night cramps following the substitution of the placebo capsule for the quinine. Quinine sulfate was again administered for one month, and by August 20, only one muscle cramp had occurred. On September 17, no night cramps were reported despite the fact that quinine sulfate had been discontinued two weeks before. This persistent relief following the discontinuation of the drug is a typical clinical effect of varied periods of quinine administration in patients with night cramps. At this time prostigmine bromide was substituted for the quinine. On September 24, no cramps had appeared following prostigmine bromide, 7.5 mg. after dinner and at bedtime. Prostigmine bromide, 15 mg. three times a day, was administered. On October 22, no cramps had been noted. The patient reported slight weakness and sweating following the use of "these capsules." The dose of prostigmine was then reduced to 7.5 mg. three times a day. On October 29, the patient reported only one slight night cramp. She volunteered the information that movement of her "stiff joints" was freer. Prostigmine was administered for more than a month with no return of the night cramps. Vitamins were administered throughout this period. During the month of December, only the yeast and thiamine were administered. In January, she reported no return of night cramps but her joints again "became stiff" following the discontinuance of prostigmine.

DISCUSSION

The theory of the chemical transmission of nerve impulses assumes the discharge of choline from nerve endings, which in turn stimulates the motor endplates in the muscle. The choline is promptly destroyed by the cholinesterase in the blood. Physostigmine and prostigmine protect the choline against destruction by this enzyme. They thus amplify or prolong the choline effect upon the muscle endplates. Quinine supposedly diminishes the sensitivity of the endplates to the stimulation of the cholinergic nerves. Notwithstanding the clinical value of this hypothesis, most investigators believe that further experimental work is necessary to establish accurately the mode and the site of the action of prostigmine and quinine. Some doubt is added by the fact that acetylcholine and acetyl-beta-methylcholine, the activity of which is protected by prostigmine, will not influence either myasthenia gravis or the myotonias.⁷

We are most concerned with quinine in this work. Though quinine salts might well antagonize prostigmine in certain diseases, they need not necessarily act at the same point. Harvey⁸ states "it is possible that the drug (quinine) exerts its influence upon both the neuromuscular junction and the muscle itself." The exact effect of quinine on isolated muscle has been shown by the nerve muscle preparation of Briscoe.⁹ Briscoe found that the perfusion of the preparation with quinine did not decrease the amplitude of contraction as much as it decreased the ability of the muscle to maintain tension upon repeated rapid stimulation. Thus, a refractory stage was created in skeletal muscle approaching that of normal heart muscle. The action is not unlike that of quinidine sulfate. Briscoe's experiments did not determine whether the myoneural junction or the muscle itself was the site of action of the quinine. Briscoe, however, compared the action of quinine to mild degrees of curarization. If her analogy is correct, further light is thrown on the point by Langley. Noting the tonic effect on skeletal

muscle when touched by nicotine, Langley^{10a} found "that this contraction is prevented by a sufficient quantity of curare; and that the action of both poisons is unaltered, in essential features, by degeneration of the nerve endings."

Our clinical observations with quinine point more toward direct action upon muscle. First, prostigmine failed to initiate or increase the frequency of muscle cramps. Second, the physiologic circumstances attending the onset of cramps seemed to be related to metabolic conditions within the muscle at the time of onset. It was pointed out earlier that 50 per cent of our patients were referred to us by the Diabetic Clinic and that the presence of vein pathology was the next most consistent finding. Most interesting was the coincidence of both intermittent claudication and night cramps in four patients. In all four of these patients, the muscle spasm at rest was completely relieved by quinine sulfate while the intermittent claudication on exertion remained unchanged. We believe that the muscle spasm in these patients resulted from the stimulation of the muscle by metabolites, which accumulated as a result of venous stasis or by the products of abnormal muscle metabolism such as is observed in patients with diabetes mellitus. The high incidence of muscle cramps in pregnant women might be associated with the increase of venous pressure in the legs and is consistent with the concept of an arteriovenous communication in the placenta. If we are correct in the assumption that metabolites stimulate the muscle and cause cramps, one should expect an increase in metabolic by-products following exercise. Almost every patient noticed that muscle cramps at night were most severe following unusual activity during the day. One woman reported that she had night cramps in the calf muscle of the legs when she worked the pedal of her sewing machine during the early evening. This finding is not inconsistent with Gootnick's¹¹ correlation of cramp and postural defect where muscular stress would necessitate increased metabolic activity. The phenomenon of spontaneous muscle contraction at rest following activity seemed so similar to rigor mortis that we investigated the onset of rigor in animals following death from air embolus or lethal doses of quinine. No differences were noted. Experiments on animals dying following violent exercise with and without previous quininization are being pursued.

CONCLUSIONS

1. Twenty patients suffering from nocturnal muscle cramps at rest were observed for a prolonged period of time.
2. Night cramps appear to result from the action of some end product of metabolism, as in diabetes, or from poor elimination of normal end products of muscle metabolism, as in patients with venous stasis due to varicose veins, pregnancy, or following deep venous occlusion.
3. Increased muscular activity favors the development of night cramps in the rest which follows such activity.
4. No etiological or therapeutic relationship exists between intermittent claudication and muscle cramps at rest.

5. Quinine sulfate has been found to give prompt relief of night cramps in extremities.

6. Evidence indicates that the action of quinine is directly on muscle, rather than on the myoneural junction.

7. Quinine sulfate produces a refractory period in skeletal muscle that is similar to the refractory period in heart muscle.

8. Prostigmine, the supposed pharmacologic antagonist of quinine, failed to increase the intensity or frequency of night cramps when administered in doses sufficient to produce the vasodilating effect of the drug.

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THE RELATION BETWEEN ARTERIAL PRESSURE AND BLOOD FLOW IN THE FOOT

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THE relationships between blood flow and arterial pressure in man have never been clearly elucidated, primarily because a satisfactory technique for raising and lowering the arterial pressure in a part, without using either vasoconstrictor drugs or intense sympathetic stimulation, or causing venous congestion, has been lacking. Because of the large surface area in relation to its total mass, the foot presents itself as an ideal anatomic subject for studying the relation between arterial pressure and blood flow in the skin. The mean arterial pressure in the foot may be doubled by standing upright. Venous congestion may be avoided by emptying the foot of its venous blood by applying to the foot a pressure which exceeds the hydrostatic venous pressure, but is well below the arterial diastolic pressure, and thus does not impede the arterial inflow. On release of this pressure, blood flows into the foot under a tremendous pressure head which is unopposed on the venous side until the foot is filled. In this study, the blood flow with the subject in the supine and erect positions was measured by means of a foot plethysmograph.

METHOD

The normal subjects were medical students and ambulatory patients without evidence of vascular disease or hypertension. Observations were made on only one patient with vascular disease. The studies were done at various times during the day, and food intake was not restricted. The room temperature varied on different days between 24.0° and 26.5° centigrade.

The plethysmograph used in this study has already been described.¹ It was bolted to the end of a hand-operated tilt table in such a manner that it could comfortably accommodate the left foot. The opening for the foot in the plethysmograph was covered with a rubber membrane, in the center of which was cemented a rubber sock. The left foot was fitted into the rubber sock, the neck of which was sufficiently redundant to fit snugly around the ankle when the

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plethysmograph was filled with water. In order to avoid trapping air around the foot in the rubber sock, the instrument was filled with water when the subject was in the erect posture, thus forcing out all the free air. Soft tissue paper was placed around the ankle at the point where the rubber made contact in order to obviate the formation of a dead space when the plethysmograph was put in different positions. The rubber membrane through which the foot entered the plethysmograph was made as rigid as possible by a felt pad backed by wood sections cut to fit the ankle. Care was taken to avoid constriction of the ankle at any point.

The plethysmographic method for determining blood flow measures the initial rapid increase in foot volume which results when a venous cuff placed on the leg just proximal to the plethysmograph is suddenly inflated to a level approximately equal to the diastolic pressure. The initial increase in foot volume was recorded on moving paper by kymograph pen resting on a Brodie bellows. It was found that a bellows with a volume capacity of 40 to 50 ml. was desirable to obtain easily measurable tracings. The bellows was calibrated by adding known amounts of water to the plethysmograph.

The water surrounding the foot was kept at the desired temperature for at least thirty minutes before the blood flow measurements were recorded. During this time the subject rested quietly in the recumbent position. The water in the plethysmograph was mixed by a small electric stirring unit.

The arterial pressure was recorded with a mercury manometer by the auscultatory method in the erect and supine positions. The arm was placed at heart level.

The foot was emptied with the subject in the supine and erect postures by air pressure suddenly applied to the interior of the water-filled plethysmograph from a large reservoir.* The pressure was kept on the foot from four to eight seconds, which proved to be long enough to empty the venous system; it was then released and the blood flow recording begun one second after the release. In the recumbent position, 50 mm. Hg of air pressure were used to empty the foot; in the erect position, 110 to 130 mm. Hg of pressure were used, depending on the subject's height. Care should be taken to have large bores in the stopcocks so that air pressure will equalize rapidly when it is introduced or released. Despite these precautions, the time required for the air to expand and escape from the plethysmograph completely is sufficiently long that a portion of the curve recorded one second after release of the air pressure is the result of air expansion and not blood flow. To correct for this artefact, it is necessary to stop the blood flow into the foot by an arterial tourniquet and then obtain curves after release of the air pressure from the plethysmograph. When the slope of this curve is subtracted from the first curve, the true blood flow, expressed in cubic centimeters of blood per minute per 100 c.c. of foot (Fig. 1), may be calculated.

The method we have described was the most convenient one devised for measuring blood flow in the erect posture, for measurements could be made

*This effectively empties the foot when the plethysmograph is filled with water. It is not effective if used as an air plethysmograph.

repeatedly during a short period of time. In order to be certain that the correction for the air pressure was a valid one, the procedure was done in such a way as to eliminate that factor. The subject was tilted into the head-down position and air pressure was applied to empty the foot; an arterial cuff was then inflated just proximal to the plethysmograph to a pressure of 300 mm. Hg, and the air pressure in the plethysmograph was released. The subject was then immediately tilted to the upright position, the arterial cuff released, and the flow of blood measured. The period of arterial occlusion did not exceed twelve to fifteen seconds, which avoided a significant amount of reactive hyperemia (Fig. 1).

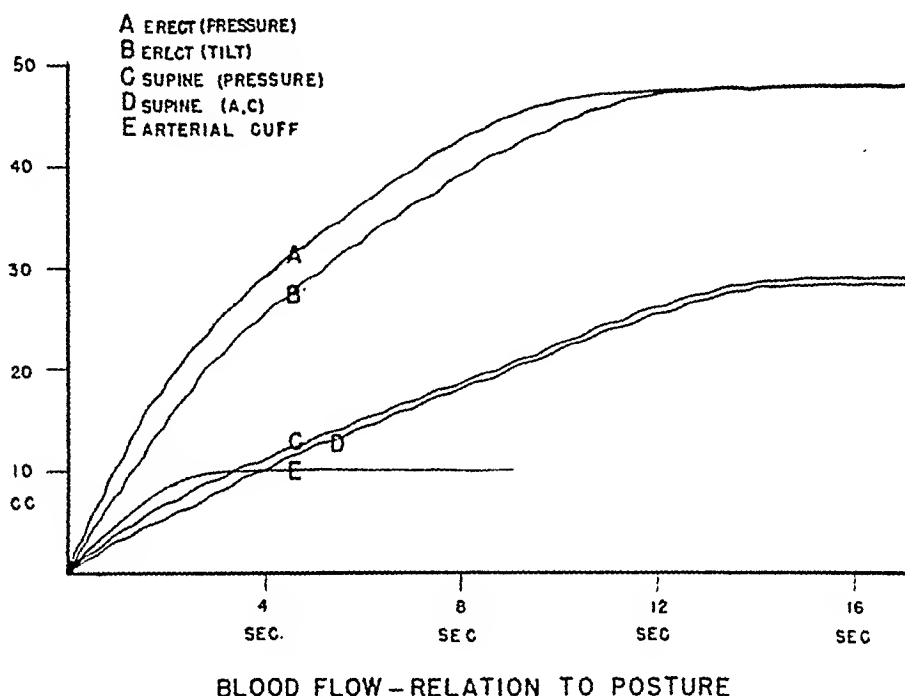


Fig. 1.—The blood flow into the emptied foot with the subject erect and recumbent (water temperature 45° C.). In this and subsequent diagrams, the ordinate is cubic centimeters and the abscissa is seconds. These figures were drawn to scale from the original tracings, with the exact time relationships indicated. The undulations in the blood flow lines indicate the arterial pulsations; they are absent in the tracings made with arterial cuff applied. Curves A and C were obtained after the foot was emptied by air pressure. Curve E is the curve of air expansion with the subject erect. Zero time on the graph is actually one second after the release of air pressure. E is subtracted from A to obtain the true blood flow. B is blood flow in the erect position, taken on release of arterial tourniquet which was applied immediately before tilting. The arterial inflow was occluded for fifteen seconds. D is the blood flow into the empty foot with the subject supine. The foot was emptied by air pressure and kept empty by the application of an arterial tourniquet. Fifteen seconds later the tourniquet was released and curve D inscribed.

Experiments were designed to determine what pressure would be required to empty the foot completely of its venous blood in the erect posture, and to determine the effect of the emptying pressure on the blood flow. A standpipe, 160 cm. in height, was fastened to the top of the plethysmograph and water was added to fill it to various heights between 110 and 135 cm., depending upon the height of the subject. The rubber tube connecting the plethysmograph to the Brodie bellows was then attached to the open top of this standpipe in such a manner that free communication existed from the interior of the plethysmograph to the bellows through the standpipe. Any change in the water level in the stand-

pipe immediately reflected itself in a rise or fall of the recording needle attached to the bellows. Blood flow determinations were then performed by suddenly applying the venous cuff, which encircled the ankle, at a pressure of 150 to 170 mm. of mercury.

The procedure for measuring blood flow during reactive hyperemia was similar to that which has been described many times.²⁻⁴ The values given in the table represent the initial inflow into the foot occurring immediately after the release of the tourniquet.

Foot volume was measured directly by water displacement.

RESULTS

Maximum Dilatation of Vessels in the Foot.—It seemed desirable to measure the effect on blood flow of increasing the blood pressure in the foot with the vessels fully dilated as well as under more normal conditions. For that reason, observations were made to determine which procedures would produce maximal vasodilatation (Table I).

TABLE I. REACTIVE HYPEREMIA. RELATIONSHIP OF BLOOD FLOW (SUPINE) TO TIME OF ARTERIAL OCCLUSION

SUBJECT	BLOOD FLOW										
	32° C.				38° C.				45° C		
	TIME OF ARTERIAL OCCLUSION (MIN.)										
	0	5	10	15	0	5	10	15	0	5	10
B. F.	1.4	4.9			8.0		12.0		13.8		13.4
D. G.	3.0			12.2	8.4		17.6		22.0	22.4	
P. C.	3.2				8.0			15.0	12.0		
R. T.	4.7		5.2	7.2	6.3		9.2		17.3	17.5	
C. L.		6.5			12.0			17.0			
McD.			9.5	15.3				16.0	17.0		
L. M.	3.9	5.9		10.5				12.0	11.0		
G. B.		6.0		10.5	4.1				12.7		
G. B.	2.3			10.2	16.0		18.0		34.0	32.8	
J. W.	2.8			8.6	6.1		10.3		15.6		
H. D.	3.0			8.3					15.6	14.9	
J. B.	3.5		9.3						13.0		13.6
E. D.	4.2								14.3		
E. S.	4.0								13.5		
J. B.	3.5										
F. R.	1.9										
P. S.	5.3										
W. M.	7.8								11.3		
E. B.	7.6										
P. P.									17.4	17.8	

All figures expressed in c.c./min./100 c.c. of foot.

Fairly complete vasodilatation has been reported as occurring in the vessels of the forearm (a muscular area) after arterial occlusion with water surrounding the arm at 32° C. for a period of five minutes.⁴ This is not true for the foot; the blood flow after arterial occlusion at 32° C. for five minutes was rarely more than 40 per cent of the maximal blood flow (Table I). Arterial occlusion at 32° C. for fifteen minutes caused a further increase in the blood flow (on the average, about 70 per cent of maximal), but it rarely produced maximal blood flow. Arterial occlusion for ten minutes, with water temperature at 38° C., produced maximal blood flow in only one of five subjects (Fig. 2). Thirty minutes' immersion of

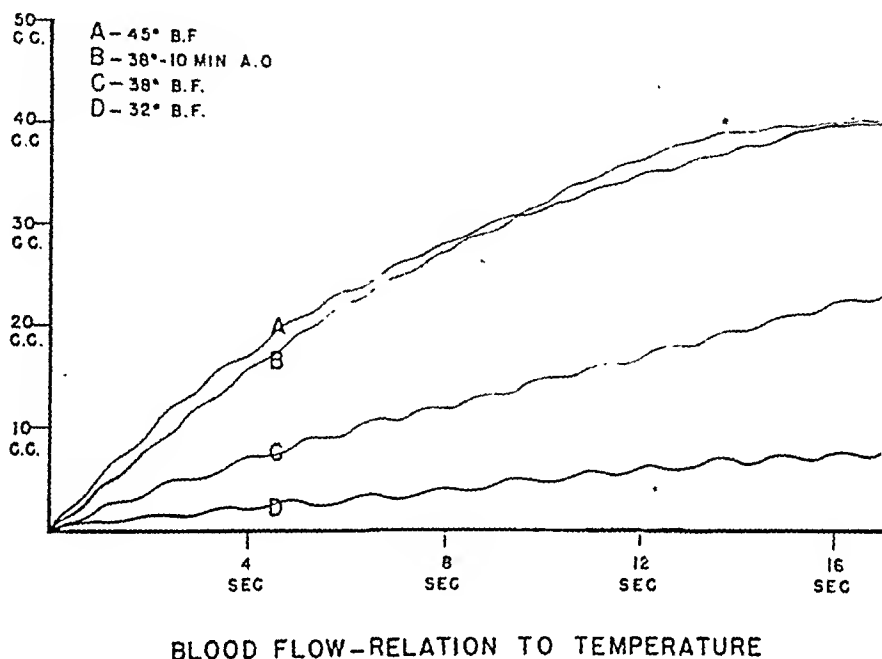


Fig. 2.—Increasing flow in the foot with increasing water temperatures. In this subject the blood flow (reactive hyperemia) at 38° C., following ten minutes arterial occlusion, is approximately equal to the blood flow at 45° centigrade. These flows were taken with the patient supine.

the foot in water at 45° C., which was as hot as the average patient could comfortably tolerate, produced maximal vasodilatation in almost 100 per cent of the subjects, as indicated by the fact that arterial occlusion produced no further increase in blood flow (Fig. 2). This had previously been demonstrated by Kunkel and Stead.⁵ There is a large variety of stimuli capable of varying the blood flow at almost any water temperature; particularly anxiety, room temperature, or discomfort. It is important, therefore, to make an effort to keep the patient as comfortable as possible and not to allow the room temperature to vary widely. It is unwise to assume that local heat has caused maximal dilatation in the foot within the the plethysmograph until the other foot has become warm from reflex vasodilation.

Effect of Emptying the Foot of Its Venous Blood With the Patient Recumbent.—When the foot is placed in the plethysmograph, varying degrees of venous congestion occur because of the pad and form around the entrance, even though an attempt is made to avoid this. The blood flow in the foot emptied of its venous

blood is faster than in the full foot at both water temperatures of 32° C. and 45° C. (Table II).

TABLE II. BLOOD FLOW IN SUPINE POSITION

SUBJECT	32° C.		45° C.	
	FOOT NOT EMPTIED	FOOT EMPTIED	FOOT NOT EMPTIED	FOOT EMPTIED
W. B.	2.6	3.7		
W. M.	7.8	8.6	11.3	14.7
E. S.	4.0	4.8	13.5	17.5
J. B.	3.5	4.9	7.5	13.8
L. C.			2.1	3.6
			(40°)*	(40°)
E. D.	4.2	5.6	14.3	19.0
P. S.	5.3	5.6		
F. R.	2.3	3.5		

All figures expressed in c.c./min./100 c.c. of foot.

*See text.

In those subjects in whom the blood flow was compared in the full and empty foot in the supine position, the following results were obtained:

The blood flows at 32° C. in the unemptied foot varied between 2.3 and 7.8 c.c. per minute per 100 c.c. of foot and between 3.5 and 8.6 c.c. in the emptied foot.

At 45° C., the blood flows in the unemptied foot varied between 7.5 and 14.3 c.c. per minute per 100 c.c. of foot and between 13.8 and 19.0 c.c. in the emptied foot.

The percentage difference at 32° C. is very nearly equal to that at 45° C., the average increases in blood flow from the full to the empty foot equalling 35 per cent and 39 per cent, respectively. The absolute difference in cubic centimeters at 32° C. is, of course, much smaller than at 45° centigrade. In comparing the blood flows in the supine and erect postures, it is advisable to compare the values for the emptied foot in both circumstances, for this obviates much of the variation in flow which occurs in the full foot (Fig. 3). The values for supine blood flows obtained at the beginning of this study were measured in feet which were not emptied, but the differences between supine and erect blood flows were of such magnitude that legitimate comparisons can still be made easily. (Those subjects in whom the foot was emptied are marked by an asterisk in Table III.)

Effect on Blood Flow of Increasing the Arterial Pressure in the Foot by Standing (Table III).—The mean arterial pressure in the recumbent position was calculated from the arithmetic mean of the values for the systolic and diastolic pressures. This value is somewhat higher than the true mean pressures. The mean pressure in the erect position was obtained by adding to the mean pressure calculated from the value obtained by the auscultatory technique the pressure of a column of water extending from the mean immersion level of the foot to the fourth rib. As the arch of the aorta extends higher than the fourth rib, the estimated pressure is probably somewhat too low. The estimated mean pressure

TABLE III. BLOOD FLOW IN C.C. PER MINUTE PER 100 C.C. OF FOOT

SUBJECT	AGE	32° C.			38° C.			45° C.			MEAN PRESSURE IN MM. HG	
		SUPINE	ERECT	STANDPIPE	SUPINE	ERECT	STANDPIPE	SUPINE	ERECT	STANDPIPE	SUPINE	ERECT
B. F.	30	1.4	13.7					13.8	31.0		95	190
P. C.	23	3.2	33.0					9.6	38.0		103	183
H. D.	30	3.0	8.3					15.6	36.0		89	169
B. P.	30	1.6	5.0	1.3							112	205
J. B.	28	3.5*	12.0					13.0	24.0		95	197
E. D.	22	5.6*	13.0	4.5				19.0*	48.0	17.8	80	180
E. S.	37	4.8*	9.5	4.0				17.5*	40.0	10.1	90	208
J. B.	22	5.0*	12.0					14.7*	47.0		94	192
F. R.	30	3.5*	9.0								96	187
P. S.	26	5.6*	12.2								88	184
W. M.	23	8.6*	17.0	6.6							91	198
E. B.†	30	15.0*	39.0								84	192
D. G.	28				8.4	33.0		22.0	44.0	21.5	108	206
R. T.	21				7.3	20.0					97	205
C. B.	27				12.0	35.0					90	191
G. B.	33				16.0	48.0		34.0	77.0	29.0	89	192
P. P.	24				2.7* (40°)	9.6 (40°)	2.6	17.4	55.0		77	178
L. C.	53										128	215

*Subjects in whom foot was emptied.

†Water temperature was at 35° centigrade.

in the foot, with the subject in the upright position, was approximately double the estimated mean pressure with the subject in the supine position (Table III).

The blood flows at 32° C. in the erect posture ranged from 5.0 to 33.0 c.c. per minute per 100 c.c. of foot. In comparing the blood flow in the erect and supine positions, only values were used where the foot had been previously emptied of blood by air pressure before the arterial inflow was recorded. The increases in blood flow in the foot at 32° C. which resulted when the subject was changed from the supine to the erect posture ranged between two and three times the original level in the supine posture. The average increase was 2.4 times the original resting blood flow in the supine position.

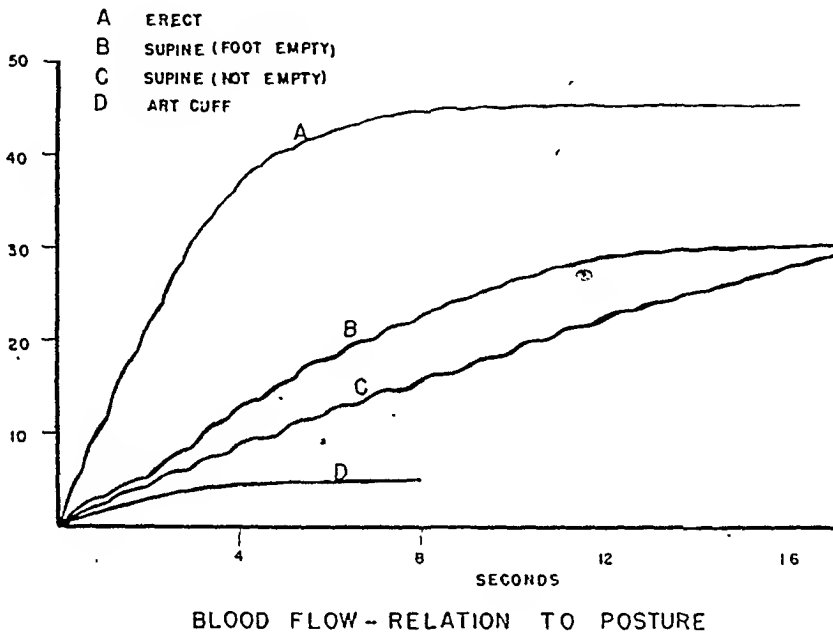


Fig. 3.—Blood flow into an unemptied and an emptied foot with subject recumbent compared with blood flow in emptied foot with subject erect. (Water temperature 45° centigrade.) *D* represents the curve of expansion of air occurring one second after release of air pressure (subject erect).

At 45° C., successive determinations in a given subject gave much more constant values than at 32° centigrade. There was still a wide variation in the values from subject to subject. The blood flow in the erect posture ranged between 24.0 and 77.0 c.c. per minute per 100 c.c. of foot. The increases resulting from assuming the erect posture ranged between two and three times the original supine level. The average increase was 2.5 times the original resting level obtained in the supine position. Again, only those observations made with the foot emptied in both the erect and recumbent positions are included.

In the four subjects, the blood flow was compared in the erect and supine postures at 38° centigrade. The blood flows in the erect posture ranged from 20 to 43 c.c. per minute per 100 c.c. of foot. As the foot was not emptied, no comparison can be made between the blood flow in the emptied foot in the erect and supine positions.

The question arose whether the rapid filling of the foot in the erect position resulted entirely from arterial inflow or from the combination of arterial inflow

and venous back flow from gravity. After the foot was emptied by air pressure, a cuff immediately proximal to the plethysmograph was inflated to 130 mm. of mercury. This was not sufficient to interfere with the arterial inflow, but it should have prevented venous back flow into the foot due to incompetent valves. The application of this cuff did not alter the rate of filling of the foot. It must be remembered that essentially normal subjects were being studied. Different results would be expected in subjects with incompetent venous valves.

The foot in the erect posture was largely emptied of venous blood by hydrostatic pressure 8 to 15 cm. greater than the venous pressure. At 32° C., the blood flow with hydrostatic pressure applied varied between 1.3 and 6.6 c.c. per minute per 100 c.c. of foot. The blood flow was not significantly different from that present with the patient in the horizontal position. Observations were made on four subjects at 45° centigrade. In three, there was no significant difference in the standing and lying positions. In the fourth, the blood flow in the erect position was reduced by the hydrostatic pressure to a level below that present with the patient supine (Table III).

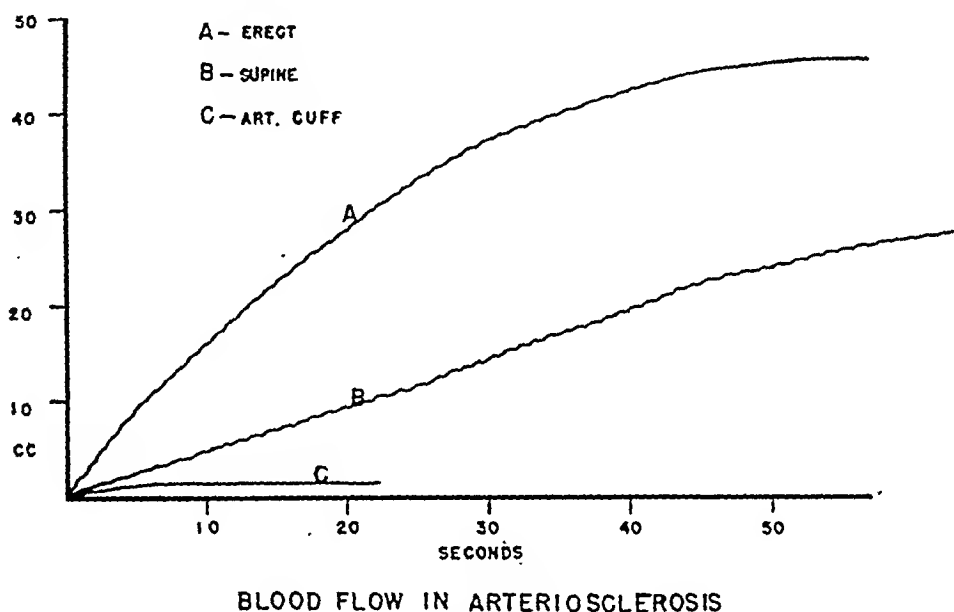


Fig. 4.—Blood flow tracings in arteriosclerosis. (Temperature of water 40° centigrade.) The dorsalis pedis, posterior tibial, and popliteal pulses were not palpable. The slow filling of the foot, even in the erect posture, is obvious. Note disappearance of arterial pulsations as foot fills.

Observations were made on three different days on one subject (L. C. in Tables II and III and Fig. 4) with moderately advanced arteriosclerosis obliterans, two weeks after a lumbar sympathectomy had been done. It seemed desirable to determine the effect of a postural increase in arterial pressure on the blood flow into a foot which was fed entirely by collateral circulation. The femoral pulse was present but the popliteal, posterior tibial, and dorsalis pedis pulses could not be felt.

He was studied at 40° C. rather than 45° C., to avoid possible tissue trauma. In a normal individual, rapid blood flow through the foot, when immersed in water at 45° C., acts as a cooling system to lower the temperature of the foot.

This cooling mechanism is greatly handicapped in the presence of obliterative vascular disease. His supine blood flow was 2.7 c.c. per minute per 100 c.c. of foot; on standing erect, the flow increased to 9.6, or about 3.5 times. The blood flow with the subject in the erect position, with pressure in the standpipe sufficient to empty the foot of its venous blood, was essentially identical with that obtained with the patient supine.

DISCUSSION

The relationship in man between the quantity of blood flowing through a part and the arterial pressure has never been thoroughly studied because of the lack of a convenient and physiologic method of increasing the arterial pressure. The observations recorded in this presentation are of interest in that they demonstrate that an increase in arterial pressure will cause an increase in blood flow through the skin, both in vessels which are partially constricted and in those which are completely dilated by heat. An increase in blood flow from a rise in arterial pressure was to be expected when the vessels were maximally dilated. The response to an increase in arterial pressure when the vessels are partially constricted could not have been predicted. On theoretical grounds it seemed possible that an increase in blood flow produced by a rise in arterial pressure might be compensated by vasoconstriction. The theory of local tissue control propounded by Lewis⁶ would lead us to expect that the increased blood flow would wash out the "H substance" from the tissues, thus causing vasoconstriction and a return of the blood flow to the level present before the rise in arterial pressure. As far as we could determine, a sustained increase in blood flow was not followed by a tendency to vasoconstriction. At the end of a five-minute period in which the foot was emptied repeatedly, the blood flow into the empty foot remained at a high level. These observations were not entirely satisfactory and they should be repeated, using a mechanical device to empty the foot rhythmically.

The increase in flow at a temperature of 32° C., produced by raising the arterial pressure, does not occur because the vessels are mechanically paralyzed by the high arterial pressure. If the foot is placed in colder water, the blood flow decreases. If it is warmed, the flow increases. It would appear that the ability of the vessels of the foot to alter their caliber in response to changes in temperature is not altered.

In a system of rigid tubes filled with a simple solution of constant viscosity, the flow varies directly with the pressure driving the fluid. If the pressure is doubled the flow is doubled. Blood is not a simple solution, and the effective viscosity may change with the velocity of flow.⁷ In our subjects the blood flow in the emptied foot was usually more than doubled when the mean pressure was doubled. Our methods of recording mean pressure and blood flow were too crude to allow us to be certain that this finding is significant. Green and collaborators,⁷ in a study of the relationship between arterial pressure and blood flow in the perfused skin and muscle of dogs, stated that during a constant state of vasomotor activity increments of blood flow per increment of perfusion pressure in skin, and often in muscle, increased regularly from zero upward when flow

was measured immediately after establishment of the perfusion pressure. Wilkins and Eichna⁸ demonstrated a rise in blood flow in the vessels of the forearm and calf dilated by a five-minute period of arterial occlusion. They found equal increments of pressure to cause equal increments in blood flow.

The demonstration that the blood flow increases as the arterial pressure rises is of interest in relation to the hemodynamics of hypertension. In a previous study,⁵ it was pointed out that in hypertension the blood flow in the foot with the vessels maximally dilated is not increased above that found in normal subjects under similar conditions. This was interpreted to mean that, in response to a stimulus for maximal vasodilatation, the vessels of the foot in patients with hypertension were incapable of dilating as fully as those of normal persons. If the hypertension were lowered by an acute infectious disease, the vessels might then respond differently and dilate as well as those of a normal subject. The assumption that hypertension would cause an abnormally high blood flow in the foot when the vessels are dilated by heat, if they could react as normal vessels, is supported by the observations recorded in this paper.

The duration of the rapid blood flow produced by emptying the foot of blood while standing erect depends on the time that it takes to fill the foot. Once the foot is full, the increase in venous pressure balances the increase in arterial pressure. Maximum flow occurs when the vessels are fully dilated and the foot is empty. As it fills, peripheral resistance increases and the blood flow diminishes. When maximal dilatation was present, the period of time in which the blood flow was increased was short, rarely exceeding six to eight seconds. When vessels were not completely dilated, the duration of increased blood flow resulting from standing erect was longer and frequently exceeded fifteen to twenty seconds.

The increase in blood flowing to the empty foot when the patient is erect demonstrates the fundamental soundness of the exercises described by Buerger¹⁰ for increasing the blood flow in the feet in persons with occlusive vascular disease. The foot is raised above the level of the heart to empty it of blood. It is then placed below heart level and the increased arterial pressure head created by gravity is unopposed for a time because the veins are empty. The flow in the foot is increased until the foot is filled. The disadvantages of these exercises lie in the fact that they can only be carried out for a relatively short time. The studies recorded in this paper suggest that a peripheral venous pump designed to empty the foot rhythmically while the patient was standing might be much more effective. The foot can be emptied in a few seconds without decreasing the flow appreciably below that normally present when the patient is lying down. During the next fifteen to forty-five seconds the foot would fill at a more rapid rate. Studies are now in progress to determine whether a peripheral venous pump has any clinical usefulness.

SUMMARY AND CONCLUSIONS

1. A method is described for measuring the arterial blood flow in the foot of the erect subject. This method primarily involves emptying the venous system of the foot by means of air pressure and recording the inflow of blood into the foot by means of a water plethysmograph.

2. Occlusion of the arterial inflow to the foot is followed by reactive hyperemia, but in order to obtain maximum dilatation with the water temperature between 32° and 38° C., the period of arterial occlusion must be much longer than is necessary to dilate the vessels in the forearm. Immersing the foot in water at 45° C. will cause complete vasodilatation.

3. The blood flow in the emptied foot with the subject erect must be compared with the blood flow in the emptied foot with the subject supine. When the patient is supine, the blood flow into the emptied foot is approximately 35 per cent faster than into the unemptied foot.

4. The mean arterial pressure in the foot is approximately doubled by motionless standing. This increase in arterial pressure when the subject is erect causes the blood flow into the emptied foot when the patient is in the upright position to be approximately twice that present under similar conditions when the subject is supine. The blood flow in the emptied foot increases when the patient is erect, both when the vessels are partly constricted by lowering the temperature and when they are completely dilated by heat.

5. The pressure required to empty the foot of its venous blood when the subject is erect does not reduce the blood flow greatly below that normally present when the subject is recumbent.

6. Observations were made on three different days in one patient with vascular disease in whom popliteal, posterior tibial, and dorsalis pedis pulses were absent. He had undergone a left paravertebral sympathectomy. The blood flow at 40° C. was about three and one-half times greater in the erect than in the supine posture.

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ELECTROCARDIOGRAM IN CHRONIC COR PULMONALE

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SINCE the publication by one of us (D. S. P.) of a paper on chronic cor pulmonale, we have become increasingly interested in the electrocardiographic features of this condition. We are now convinced that the electrogram is a real aid in the diagnosis of chronic cor pulmonale, and that frequently a diagnosis of this condition can be made by the electrocardiogram before it can be made by clinical methods.

In order to gain a better knowledge of the electrocardiogram in this condition, we have studied fifty cases of chronic cor pulmonale in which the diagnosis was confirmed by the clinical, x-ray, and electrocardiographic findings.

STANDARD LEADS AND UNIPOLAR EXTREMITY LEADS

P Wave.—In chronic cor pulmonale the P wave is usually higher than normal, particularly in Leads II and III (Table I, Figs. 1 and 2). In our series, the highest voltage was 3.7 mm. for P_2 and 3.0 mm. for P_3 . The voltage and width of P_1 was not significantly altered. We believe that when the voltage of P_2 or P_3 is below 0.5 mm. the possibility of uncomplicated chronic cor pulmonale is practically excluded. Only one case in our series had such findings, and this case presented aortic atheroma as a complication.

When the net area of P_3 is greater than that of P_1 , the mean manifest axis of P (\hat{A}_P) will be to the right of $+60^\circ$. Fig. 7 shows that all but eight cases had an \hat{A}_P of $+60^\circ$ or more, with an average of $+69^\circ$. This figure would be increased to 71.6° had the case shown in Table I been excluded. In either event, the average is to the right of that found by Novelo² ($+64^\circ$). In our series, the magnitude of \hat{A}_P varies from 0.5 to 4.2 Ashman units, with an average of 2.36 units. We do not know the normal magnitude of \hat{A}_P .

The P in Lead V_F was positive in 97.9 per cent of the cases, diphasic in 2.08 per cent (only one case), and negative in no case (Fig. 3).

Our values for the voltage of P in Lead V_F are above the normal ones, if we calculate these values from the formula $V_F = \frac{\text{Lead II and Lead III}}{3}$. A histo-

gram of the voltages of the P in Lead V_F is very similar to that of P_3 . We think that a small or absent P in the V_F -lead can exclude the possibility of chronic

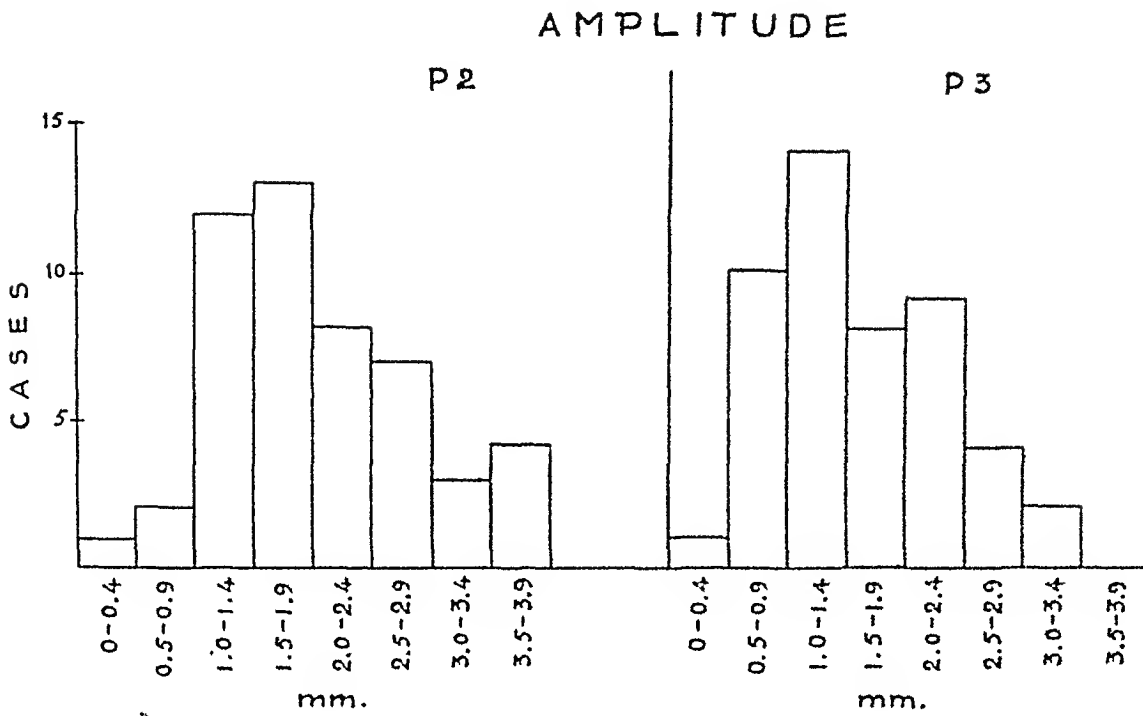


Fig. 1.

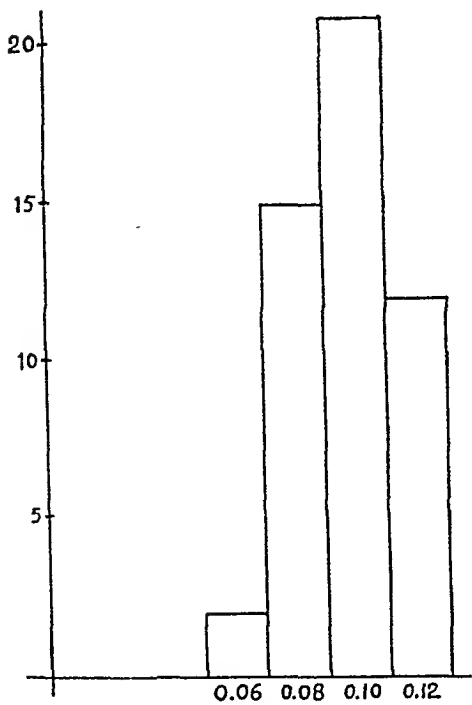


Fig. 2.

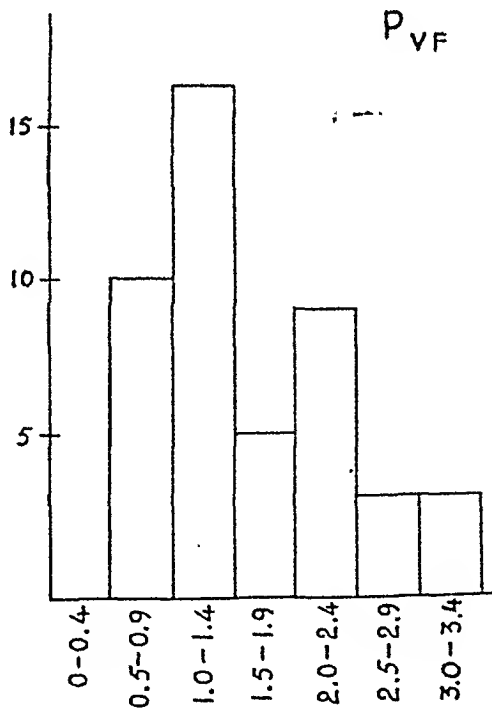


Fig. 3.

Figs. 1, 2, and 3.—Amplitude and width of the P wave in Leads II, III, and V_F. The P wave is higher than normal in 4 per cent of the cases in Lead II, in 30 per cent in Lead III, and in 40 per cent in Lead V_F. The width of P shows no significant changes.

cor pulmonale more readily than a high P in this lead can establish the diagnosis of such a condition, because some cases of congenital heart disease and rheumatic heart disease with tricuspid involvement can also present a high P in the V_F lead.

TABLE I. AMPLITUDE AND WIDTH OF THE P WAVES

	COR PULMONALE		NORMAL*
	AMPLITUDE (MM.)	WIDTH (SEC.)	AMPLITUDE (MM.)
P_1			
Max.	1.8	0.12	1.1
Med.	0.6	0.06	0.55
Min.	0	0	0
P_2			
Max.	3.7	0.12	2.5
Med.	1.9	0.09	1.25
Min.	0.8	0.04	0.3
P_3			
Max.	3.0	0.12	2.0
Med.	1.4	0.08	0.8
Min.	0.5	0.04	-1.0
P_{VF}			
Max.	2.13		1.5†
Med.	1.0		0.68
Min.	0.33		-0.23

One case complicated with aortic atheroma ($P_2 = 0$ and $P_3 = -0.5$ mm.).

*According to Ashman and Hull.⁹

†Calculated from formula $V_F = \frac{D_2 + D_3}{3}$.

In a previous paper,¹ the great frequency of a negative P in Lead V_L was mentioned. In the present series (Table II), the P wave of Lead V_L was negative in 54.4 per cent of the cases, diphasic with a preponderance of the negative phase in 13.1 per cent, isodiphasic in 8.7 per cent, isoelectric in 6.5 per cent, and predominantly positive in 17.2 per cent. The P in this lead is frequently negative; but, when this sign is found alone, it is of secondary importance. On the other hand, we must emphasize the infrequency (17.2 per cent) of a positive P in the V_L lead in chronic cor pulmonale.

According to the shape of the P wave, we divided them into two main groups: "gothic" form (58 per cent) where the apex of the P wave was pointed, and the "romanesque" form (42 per cent) where the apex of the P wave was round.

Auricular T Wave.—The auricular repolarization wave (T_A) manifests itself as a slightly negative phase which follows the P wave. This wave is not easily detected because of its smallness or because it is superimposed on the QRS complex. In certain abnormal conditions, the P-R segment can show a negative displacement of 1 mm. or more. This could be related to disturbances of auricu-

lar repolarization, because of its similarity to the experimental tracings obtained when the auricular muscle is injured.

TABLE II. THE P WAVE IN LEAD V_L

DIRECTION	NUMBER OF CASES	PER CENT
-	25	54.4
+	5	10.9
+	1	2.2
-		67.5
+	4	8.7
±	0	0
0	3	6.5
		15.2
++	1	2.2
+		17.2
(Flat)	7	15.0

We use the terms "primary T_A " and "secondary T_A ," after Wilson's terminology, in cases where the ventricular T wave changes. This author calls the changes "primary" when they are due to abnormal ventricular repolarization (myocardial damage) and "secondary" when they depend on a modification of the ventricular depolarization (ventricular hypertrophy and bundle branch block). We apply the term "secondary T_A " when a negative displacement of the P-R segment accompanies a P wave of high voltage (due to auricular hypertrophy); the term "primary T_A " is applied to a negative displacement of the P-R interval when it follows a notched P wave of normal or low voltage (due to auricular damage). In our series of cases (Fig. 4, and Table III), there was fre-

TABLE III. DISPLACEMENT OF THE P-R SEGMENT (AURICULAR T WAVE)

	NORMAL (MM.)	COR PULMONALE (MM.)
Min.	0	0
Med.	0.25	0.5
Max.	0.5	1.2

quently a negative displacement of the P-R segment in Leads II and III, which varied from 0 to 1.2 mm., with an average of 0.5 millimeter. These figures are above those given for normal individuals: 0.25 mm., average, and 0.5 mm., maximum. It is probable that most of our cases exhibited "secondary T_A "

and few of them "primary T_A ," since the abnormal P-R segment is usually associated with high voltage P waves.

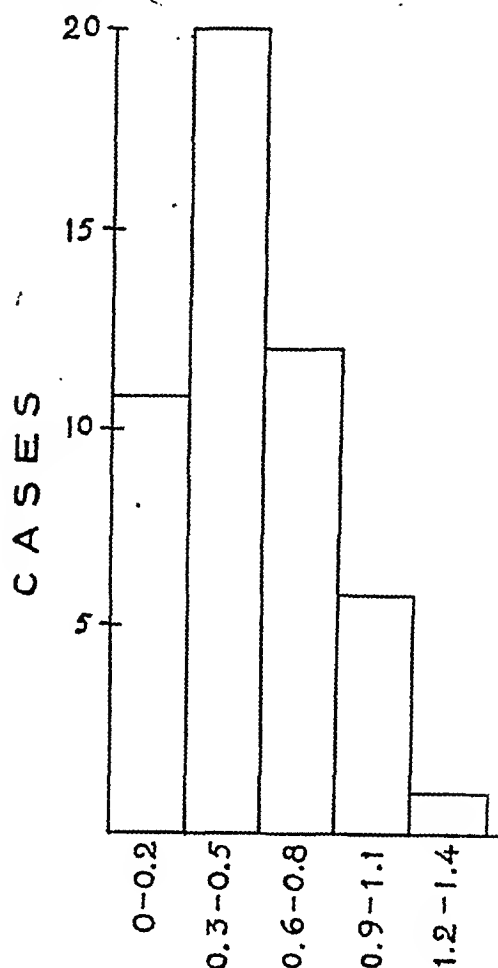


Fig. 4.—P-R segment. The negative displacement of the P-R segment exhibits a "secondary" auricular T wave, due to auricular hypertrophy.

P-R Interval.—The P-R interval was normal in every case. Therefore, the possibility of some complication (digitalis action, rheumatic heart disease, vagotonia, myocardial sclerosis, and so forth) must be investigated in patients with chronic cor pulmonale who show first degree A-V heart block.

Q and S Waves.—The high incidence of an S_1 - Q_3 pattern and the rarity of a Q_1 - S_3 pattern has been pointed out.¹ This was confirmed in our series: S_1 was present in 96 per cent, and Q_3 , in 68 per cent of the cases (Fig. 5). One case showed a Q_1 - Q_2 - Q_3 pattern and eleven (22 per cent) cases showed an S_1 - S_2 - S_3 pattern. Meek and Wilson³ have emphasized the presence of an S_1 - Q_3 pattern in hearts with a clockwise rotation about their anatomic axis. In our cases such a rotation was more frequent (62 per cent) than among normal persons (29 per cent) (Table IV). If we diagnose a backward position of the apex of the heart in those cases having an S_1 - S_2 - S_3 , as well as in those with S_1 - S_2 pattern, who present marked clockwise rotation, the percentage of such a rotation (29 per cent) rises to 46 per cent, which is well above the figure among normal hearts.

R and S Waves.—The voltage of these waves is shown in Fig. 6. The average of the R wave (particularly R_1) was below normal (Table V). S_1 was greater and S_3 less than normal. The combination $R_1 < R_2 < R_3$ was present in 62 per cent of the cases, and that of $S_1 > S_2 > S_3$ was even more frequent (84 per cent). The association of both is considered abnormal by Holzmänn⁴ (pathologic dextro-type).

TABLE IV. ROTATION OF THE HEART ABOUT THE LONGITUDINAL AXIS

	NORMAL (PER CENT OF CASES)	COR PULMONALE (PER CENT OF CASES)
Clockwise	29	60
Counterclockwise	16	2
Without rotation	55	38

TABLE V. AVERAGE VALUES OF R AND S IN THE LIMB LEADS

	NORMAL* (MM.)	COR PULMONALE (MM.)
R_1	6.81	1.61
R_2	11.99	4.14
R_3	8.5	5.58
S_1	1.67	3.71
S_2	1.53	2.12
S_3	1.27	0.68

*According to Kossmann and Johnston.¹⁰

RS-T Segment and T Wave.—The RS-T segment (particularly in Leads II, III, and V_F) frequently (66.6 per cent) showed a negative displacement; it was sometimes isoelectric (27.8 per cent), and rarely positive (5.53 per cent). One-half of the cases with negative displacement showed a "staircase" shape (the RS-T segment parallel to the isoelectric line, but below it); the other half showed a downward slope of the RS-T segment, with a T wave which was either negative or diphasic. Negative (16 per cent), diphasic ($- +$) (48 per cent), and flat (18 per cent) T waves were mainly found in Leads III and V_F . The wave was positive in these leads only in a few cases (18 per cent) (Table VI). We emphasize that a diphasic T_3 of the $- +$ type was more often seen than a negative T_3 , which is usually considered one of the principal characteristics of chronic cor pulmonale. We do not know whether this diphasic T_3 was due to right ventricular hypertrophy, myocardial damage, or position of the heart. The presence of a negative T wave in Leads III and V_F in normal vertical hearts

with a forward position of the apex and clockwise rotation about their anatomic axis has been recently mentioned by Goldberger.⁶

Another QRS-T pattern was seen in Lead III with some frequency, but cannot be considered as pathognomonic of chronic cor pulmonale. It consisted of

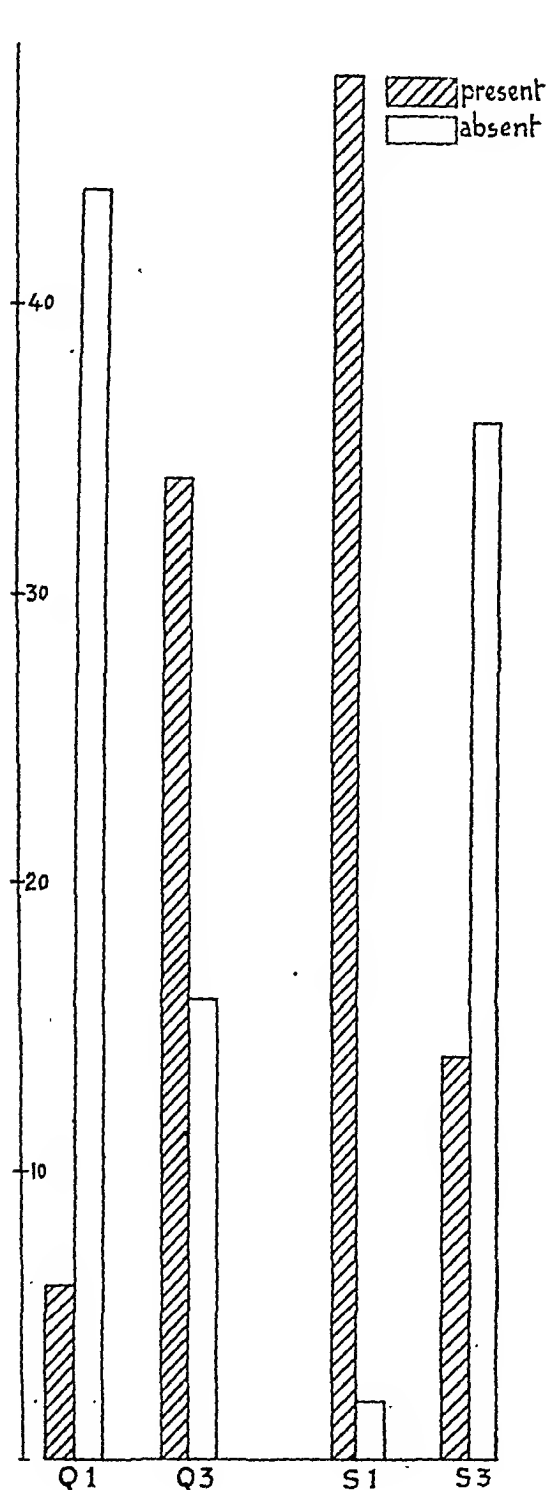


Fig. 5.

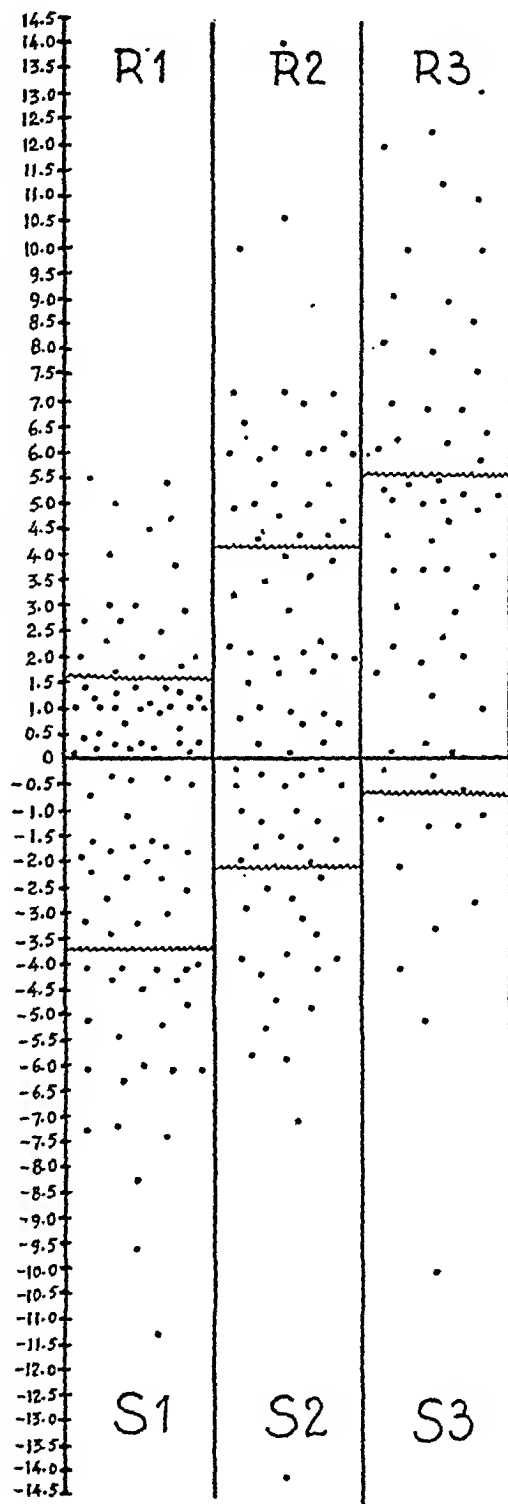


Fig. 6.

Fig. 5.—Q and S waves in the limb leads. Presence of S_1 in 96 per cent and of Q_3 in 68 per cent of the cases. Absence of Q_1 in 88 per cent and of S_3 in 72 per cent of the cases.

Fig. 6.—Amplitude of the R and S waves in the limb leads. Notice the small voltage of R_1 and S_2 in comparison with the high voltage of R_3 and S_1 . For average values, see Table V.

(a) a small Q wave, (b) a high R wave ($R_3 > R_2 > R_1$), (c) a small or absent S wave, and (d) a "staircase" RS-T segment.

TABLE VI. DIRECTION OF RS-T SEGMENT AND T WAVE

	CASES	PER CENT
Lead I		
+	44	88
0	6	12
-	0	0
Lead III		
+	9	18
0	9	18
-+	24	48
-	8	16

Mean Manifest Axis of QRS (\hat{A}_{QRS}).—In our cases, \hat{A}_{QRS} lay on Bayley's Sextants 2, 3, 4, and 5, and every case except two fell between $+90^\circ$ and -90° (Fig. 7); the same distribution was found in a previous study of right ventricular hypertrophy.⁵ We do not remember a case of pure chronic cor pulmonale (not complicated by *cor aortale*) which had its \hat{A}_{QRS} on Sextants 1 or 6.

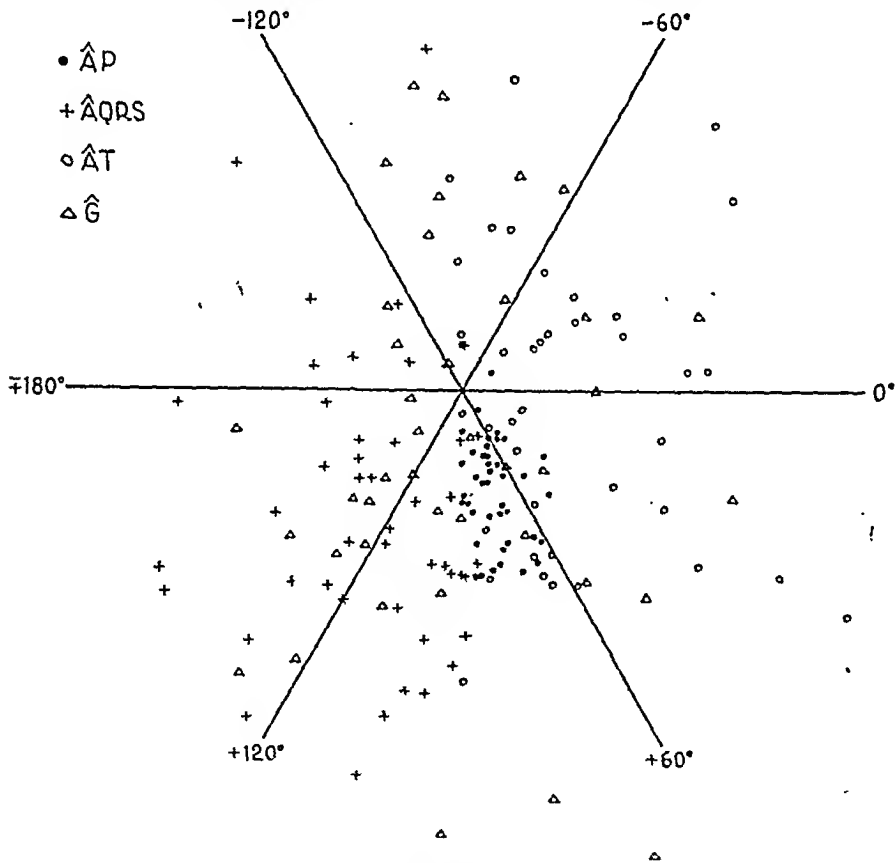


Fig. 7.—The mean manifest axis. \hat{A}_P is to the right of $+60^\circ$, with an average of 71.6° . \hat{A}_{QRS} falls between $+90^\circ$ and -90° , in Bayley's Sextants 2,3,4, and 5. \hat{A}_T lies on Sextants 1,2,5, and 6 between $+90^\circ$ and -90° . G is distributed all over the system of Bayley with a certain predilection for Sextants 2,4, and 5.

Chronic cor pulmonale probably reduces the projection of the spatial vector $S\hat{A}_{QRS}$ upon the frontal plane, as compared with normal cases (Table VII). Forty per cent of our cases had a magnitude of \hat{A}_{QRS} below the lower normal value, and none exceeded the upper normal.

TABLE VII. MAGNITUDE OF \hat{A}_{QRS} AND G

	\hat{A}_{QRS}		G	
	NORMAL*	C.C.P.	NORMAL*	C.C.P.
Min.	3.5	1.0	2.5	0.6
Med.	6.3	4.46	13.0	4.53
Max.	12.0	9.0	23.0	12.5

*According to Ashman and Hull.⁹

Mean Manifest Axis of T (\hat{A}_T).—These lay on Sextants 1, 2, 5, and 6, between $+90^\circ$ and -90° (Fig. 7) (a fact which makes obvious their opposition to \hat{A}_{QRS}). This finding suggests "secondary" changes of T.

Ventricular Gradient (G).—The position of G varied greatly. It was distributed all over the system of Bayley, with a certain predilection for Sextants 2, 4, and 5 (Fig. 7). The mean magnitude of G was below normal values (Table VII). We do not know whether this was due to a peculiar position of the spatial vector SG or to an actual shortening of it.

The White-Bock Index: $(U_1 + D_3) - (D_1 + U_3)$.—This index gave normal figures in every case except three whose indices were below normal values (-16 , -18 , and -20 millimeters). Still, there was a preponderance of negative figures (Fig. 8).

Electrical Position of the Heart.—We divided our cases in two groups, according to Goldberger and Schwartz's classification⁶: vertical hearts (88 per cent), and horizontal hearts (2 per cent); in 10 per cent of the cases the electrical position could not be determined.

We shall only describe the vertical group, which was divided into three subgroups: (a) *apex forward* (twenty-nine cases); (b) *apex backward* (six cases); and (c) *apex intermediate* (nine cases).

Subgroup *a* showed a minimal dispersion of \hat{A}_{QRS} and a maximal dispersion of \hat{A}_T . Subgroup *b* showed a maximal dispersion of \hat{A}_{QRS} and a minimal dispersion of \hat{A}_T . Subgroup *c*, with an intermediate anatomic position, showed intermediate grades of dispersion of \hat{A}_{QRS} and \hat{A}_T (Fig. 9). These characteristics were probably due to a spatial relation among $S\hat{A}_{QRS}$, $S\hat{A}_T$, and SH, as well as to the spatial relations between the frontal plane and the first two vectors (see Discussion).

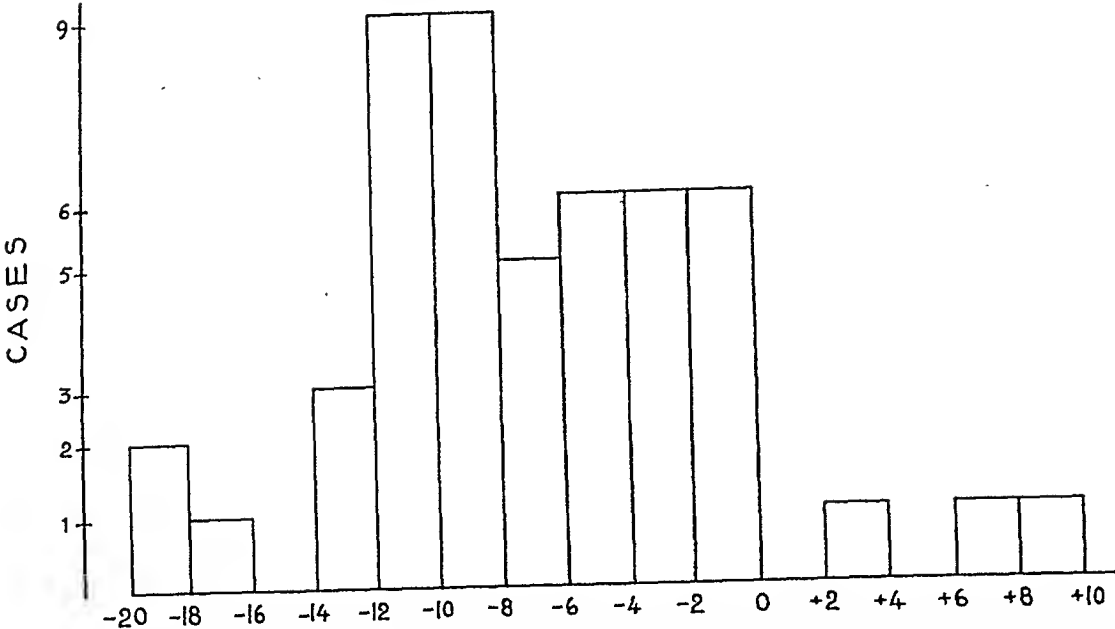


Fig. 8.—The White-Bock index. The index $(U_1 + D_3) - (D_1 + U_3)$ gives a preponderance of negative values, ranging from + 8.5 to - 19.0 (average of - 4.63). Eighty-two per cent of the cases lie between 0 and - 12.

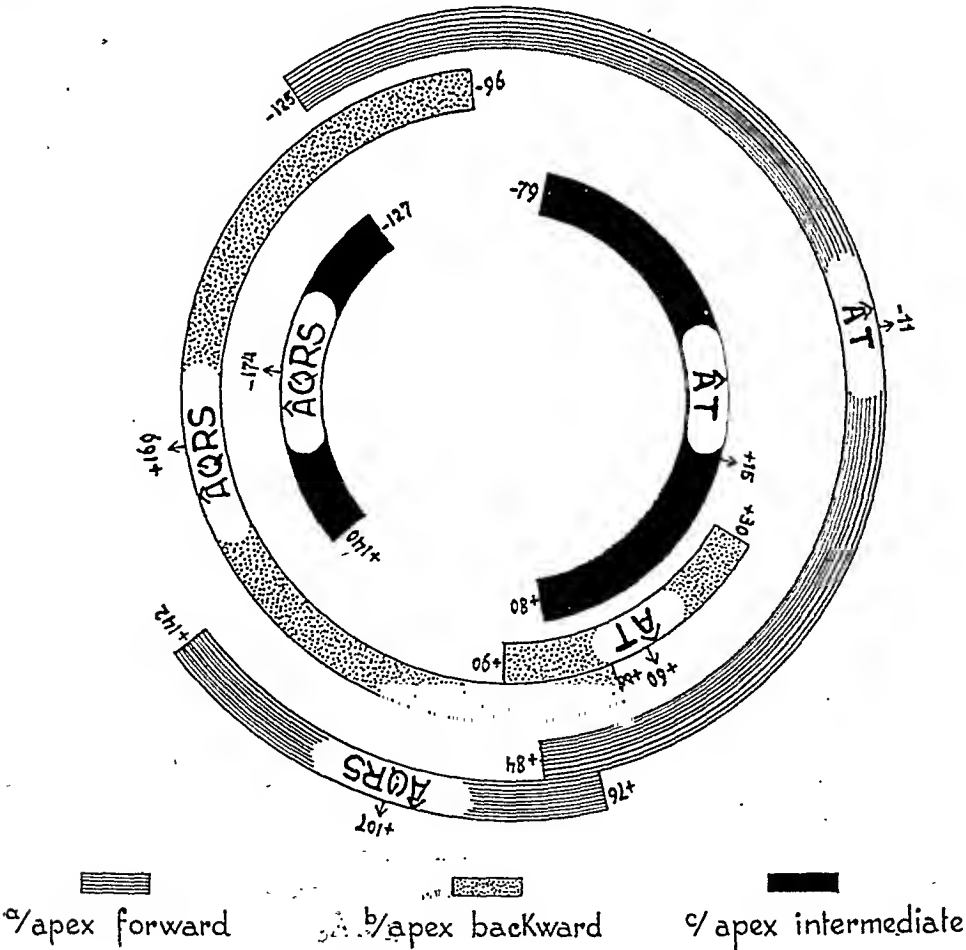


Fig. 9.—Relation between \hat{A}_{QRS} and \hat{A}_T in vertical hearts. *a*, Apex forward: minimal dispersion of \hat{A}_{QRS} and maximal dispersion of \hat{A}_T . *b*, Apex backward: maximal dispersion of \hat{A}_{QRS} and minimal of \hat{A}_T . *c*, Apex intermediate, intermediate grades of dispersion of \hat{A}_{QRS} and \hat{A}_T .

Subgroup *a* presented an endocardial pattern which appeared frequently in Lead V_R and always in Lead V_L ; this is in accordance with Goldberger's findings.⁶ Against Goldberger's expectations, only one case in subgroup *b* showed posterior epicardial pattern of the QR type in Leads V_R and V_L . A great number of cases in subgroup *c* showed a ventricular complex of the qR type in Lead V_R . This qR complex must probably be considered the result of a semidirect lead from the right auricle in cases of right ventricular hypertrophy, and not Goldberger's left ventricular epicardial pattern.

PRECARDIAL LEADS

P Wave.—A diphasic P wave was usually seen in Leads V_1 through V_3 , but was rare in Leads V_4 through V_6 (Table VIII). According to the form of this diphasic wave we speak of P waves of the + −, ++ −, or + − − type, mentioned in order of their frequency. There were some negative P waves in the right precordial leads, but they were never found beyond the V_3 position. The negative P waves described by some authors⁷ as being present all over the precordium are probably due to the use of the left leg as an "indifferent" electrode (high P in Lead V_F). As a whole, the changes of the precordial P waves are less significant than those of the standard and unipolar extremity leads.

R and S Waves.—The average voltage of R in Leads V_2 through V_6 was low, and that of S was high in Leads V_3 through V_6 (Table IX and Fig. 10). The average voltage of R + S was normal in cases of chronic cor pulmonale; this suggests a change in the position of the heart rather than an extracardiac factor (pulmonary emphysema) as a cause for the low voltage of R.

TABLE VIII. PRECORDIAL P WAVES

	+	++ −	+ −	FLAT	+ − −	−	BIFID FLAT	FLAT AND NOTCHED
V_1	8	7	16	0	6	8	3	0
V_2	11	6	17	0	3	7	5	0
V_3	21	0	7	7	1	1	8	3
V_4	20	0	1	13	1	0	7	8
V_5	17	0	0	18	1	0	1	11
V_6	15	0	0	22	1	0	0	11

T Wave.—A negative T wave was found in 59 per cent of cases in Lead V_1 , and in 46 per cent in Leads V_1 and V_2 . The T wave was usually positive in Leads V_3 through V_6 (Table X). A negative T wave in a precordial lead was always accompanied by negative T waves in the preceding precordial leads. The intrinsic deflection of Leads V_1 and V_2 was delayed in only 30 per cent of cases with a negative T wave in such leads.

TABLE IX. R AND S WAVES IN THE PRECORDIAL LEADS .

		R		S	
		NORMAL* (MM.)	C.C.P. (MM.)	NORMAL* (MM.)	C.C.P. (MM.)
V ₁	Max.	9.6	21.6	24.0	30.0
	Med.	4.16	3.9	11.05	9.3
	Min.	1.0	0.0	3.4	0.0
V ₂	Max.	20.8	18.6	38.8	51.0
	Med.	9.05	4.5	16.23	15.9
	Min.	4.0	0.0	3.0	0.0
V ₃	Max.	54.6	40.5	22.0	48.6
	Med.	16.7	5.4	9.05	22.8
	Min.	6.0	0.0	0.0	0.0
V ₄	Max.	46.0	42.0	16.0	49.5
	Med.	22.31	8.4	5.32	19.8
	Min.	12.2	0.0	0.0	0.0
V ₅	Max.	33.0	39.9	9.6	34.5
	Med.	18.78	9.9	1.93	12.3
	Min.	8.8	0.0	0.0	0.0
V ₆	Max.		36.0		22.5
	Med.		7.8		7.5
	Min.		0.3		0.0

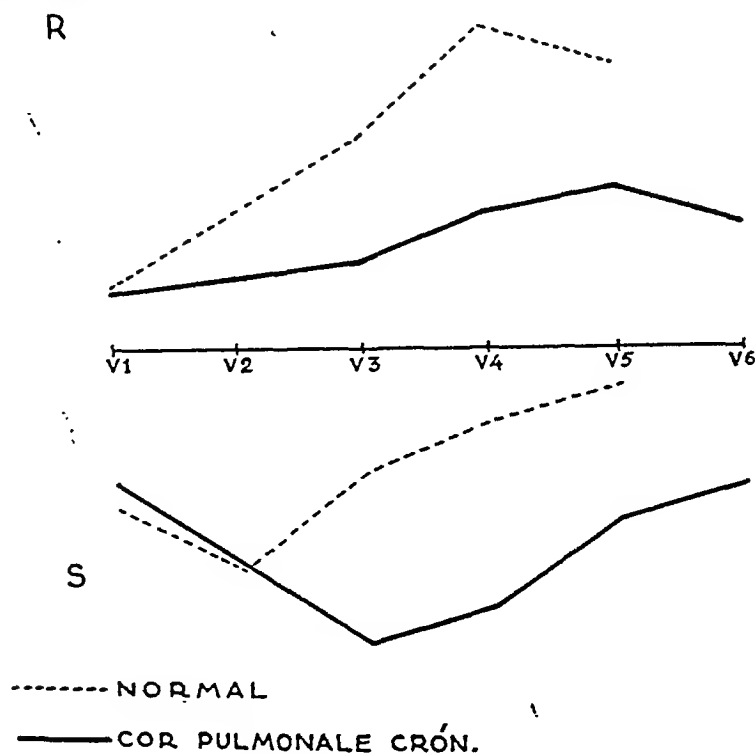
*Kossmann and Johnston.¹⁰

Fig. 10.—Precordial R and S waves. Low voltage of R and high voltage of S. The average voltage of R + S is essentially normal.

The Intrinsic Deflection of Right Precordial Leads.—Its delay was less frequent (fourteen cases) than we should expect, a priori. Five of these fourteen cases had a complication that by itself could explain the delay of the intrinsic deflection. These complications were mitral stenosis, tricuspid insufficiency, mitral calcification, aortic aneurysm with compression of the pulmonary artery, and aneurysmal dilatation of the pulmonary artery. These delayed deflections were present very frequently in ventricular complexes of the qR type (76.9 per cent), even though a qR complex was rather rare in Leads V_1 and V_2 .

TABLE X. PRECORDIAL T WAVES

	+	—	±	FLAT
V_1	9	29 (59 per cent)	3	8
V_2	16 (32 per cent)	23 (46 per cent)	4	7
V_3	24 (49 per cent)	13 (26.5 per cent)	1	11
V_4	28 (56 per cent)	8	1	13
V_5	26 (53 per cent)	4	1 (±)	18
V_6	31 (62 per cent)	1	0	18

Cor Pulmonale With Cor Aortale.—Rarely is there a small (less than 1.0 mm.) or absent S wave in Leads V_5 or V_6 . Such a condition was found in twelve cases (24 per cent) and nine of them (75 per cent) showed the following complications of the "cor aortale" type: aortic sclerosis; cardiac sclerosis; coronary heart disease; chronic myocarditis; arteriosclerosis; essential hypertension; aortic atheroma; aortic sclerosis; and arterial hypertension. On the other hand, only 15.7 per cent of cases with an S wave of more than 1.0 mm. in Leads V_5 or V_6 were complicated by "cor aortale."

DISCUSSION

Chronic cor pulmonale may give a large number of electrocardiographic changes in the limb as well as in the precordial leads. These changes are difficult to evaluate, so we shall discuss them separately first, and then consider the changes seen in chronic cor pulmonale as a whole.

The right deviation and increase of \hat{A}_P could readily be ascribed to right auricular hypertrophy, but the direction of \hat{A}_P is evidently influenced by the position of the heart, and P can augment its voltage in a reversible, transitory way. We have already mentioned the difficulty in considering a prominent T_A as "primary" or "secondary" in origin.

The changes of the precordial P waves are not necessarily due to auricular abnormalities. The descent of the diaphragm in an emphysematous patient lowers the heart and leaves the precordial positions C_1 and C_2 in a relatively higher position, thus producing a negativity in the final portion of the P wave.

A right deviation of \hat{A}_{QRS} is too readily ascribed to right ventricular hypertrophy. We believe it is the result of clockwise rotation of the heart about SH, whether this is produced by right ventricular dilatation (which so often accompanies right ventricular hypertrophy) or is merely the result of a vertical position of the heart.

The smallness of \hat{A}_{QRS} and G could be related to ventricular myocardial damage, but we must not forget the influence of the conducting medium (emphysematous lungs) and the even more important influence of a backward displacement of the heart's apex, which makes $S\hat{A}_{QRS}$ lie perpendicular to the frontal plane. The smallness of R in the precordial leads is accompanied by normal R + S voltages, thus making it unsafe to use the term "low voltage" for the precordial leads.

We must be cautious in our interpretation, even when we find a delayed intrinsic deflection. The difficulty in detecting the intrinsic deflection in the right precordial leads has been mentioned in a previous paper.⁸ The normally delayed activation of the pulmonary conus could give a delayed intrinsic deflection in Leads V_1 or V_2 in certain cases in which the heart is ptosed or the pulmonary conus dilated. Under such circumstances, a delayed intrinsic deflection could not be considered to be the direct result of right ventricular hypertrophy. We wish to emphasize that a delayed intrinsic deflection in chronic cor pulmonale may frequently be due to a complication affecting the right ventricle, as well as to the pulmonary condition.

A negative T_3 could be due to myocardial damage, but we have to remember its presence in normal hearts, and the fact that this wave can be made negative by nothing more than lowering of the diaphragm (deep inspiratory movement). Right ventricular hypertrophy may produce a negative displacement of RS- T_2 and RS- T_3 , but such displacement, when slight, might be normal and possibly related to a vertical position of the heart.

We believe that a negative T wave in the right precordial leads is largely due to the position of the heart and not entirely to right ventricular hypertrophy, because of the low incidence of a delayed intrinsic deflection accompanying such negative T waves.

It is probable that the changes of R and S in the precordial leads are due to a clockwise rotation of the heart about SH, because (1) of the higher incidence of this type of rotation in chronic cor pulmonale (62 per cent against 29 per cent in normal hearts), and (2) of the frequent finding of transitional complexes which are shifted to the left and are found in Leads V_5 or V_6 instead of in Lead V_3 as is normal.

In relation to the form of dispersion of \hat{A}_{QRS} and \hat{A}_T , let us remember that a backward situation of the apex makes $S\hat{A}_{QRS}$ lie roughly perpendicular to the frontal plane, so a greater dispersion of \hat{A}_{QRS} is to be expected. The inverse relation between the dispersion of \hat{A}_{QRS} and that of \hat{A}_T suggests that, at least in chronic cor pulmonale, the corresponding spatial vectors are perpendicular to each other.

It follows from these considerations that the position of the heart greatly influences the shape of the electrocardiogram in chronic cor pulmonale. The position which the heart assumes is determined originally by the pulmonary emphysema, and later, by the strain which the right cavities undergo.

Pulmonary emphysema has several definite effects upon the heart: It causes the heart (1) to assume a vertical position, and (2) to descend as a result of the lowering of the diaphragm; (3) it produces clockwise rotation of the heart about SH, and (4) backward displacement of the apex; (5) it also produces disturbance in the transmission of the electrical potential of the heart.

1. The vertical position of the heart produces a slight deviation of \hat{A}_{QRS} and \hat{A}_P to the right, with subsequent increase of the P wave in Leads II, III, and V_F , and causes the P wave of Lead V_L to become negative.

2. The descent of the heart contributes to the appearance in the first two precordial leads of a negative T wave, a diphasic or negative P, and possibly a late R_2 due to activation of the pulmonary conus.

3. The clockwise rotation of the heart about SH produces a considerable deviation of \hat{A}_{QRS} to the right with the appearance of an S_1-Q_3 pattern, negative values of the White-Bock index, disappearance of S_3 , transitional shape of the ventricular complexes in V_5 and V_6 (with lowering of R and deepening of S), and negativity of T_3 and the RS-T segments in Leads II, III, and V_F .

4. The backward displacement of the heart's apex gives diphasic complexes in the limb leads, and small \hat{A}_{QRS} and G, and exaggerates any deviation of \hat{A}_{QRS} which may exist.

5. The disturbance in the transmission of the heart's potential, due to the pulmonary condition, might explain the smallness of \hat{A}_{QRS} and G.

Strain on the right cavities exaggerates almost every change produced by the position of the heart, and produces new modifications of its own. Hypertrophy of the right cavities accentuates the right deviation of \hat{A}_P and \hat{A}_{QRS} , the voltage of P in Leads II, III, and V_F , as well as that of S_1 and Q_3 , the negativity of P in Leads V_L and in the precordial leads, the negative value of the White-Bock index, the smallness of R in V_5 and V_6 , the depth of S in these leads, the negativity of T in Leads III, V_1 and V_2 , and finally that of S-T in Leads II, III, and V_F . Strain of the right cavities by itself produces notching and slurring of P, possible widening of P, and delay of the intrinsic deflection.

If the electrocardiogram shows only the signs of a change in position of the heart, it is unsafe to speak of cor pulmonale; even though the pulmonary emphysema has affected the heart to the extent that it has changed its position, it may not yet have produced heart disease. If the electrocardiogram shows the signs of strain upon the right cavities (whether these are functionally sufficient or insufficient), we can speak of cor pulmonale because there is then a relationship between pneumopathy and cardiopathy.

Unfortunately, almost every change of the electrocardiogram of chronic cor pulmonale with only differences of grade can be produced by alteration of the position of the heart, as well as by the strain upon the right cavities. The final interpretation of the electrocardiographic findings rests upon the experience of the interpreter of the electrocardiogram.

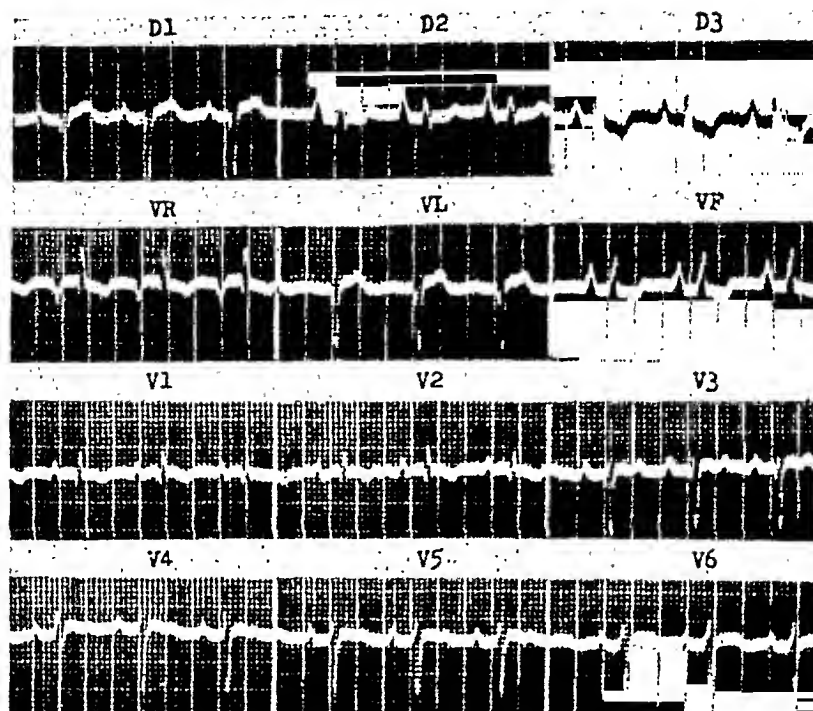


Fig. 11.—This is a typical tracing of chronic cor pulmonale. Notice the signs of right auricular hypertrophy ($\hat{A}P = +65^\circ$; $P_2 = 3.7$ mm.; gothic P wave in Leads II, III, and V_F ; diphasic P wave in V_1 and V_2 ; prominent auricular T wave in Leads II and V_F) and those of right ventricular hypertrophy ($\hat{A}QRS = +140^\circ$; qR complex in V_R and V_L ; delayed intrinsic deflection in V_L ; deep S wave in V_5 and V_6 ; small R wave from V_3 to V_6 ; negative T wave in Lead III, V_1 and V_2 ; diphasic ST-T in Leads II and V_F).

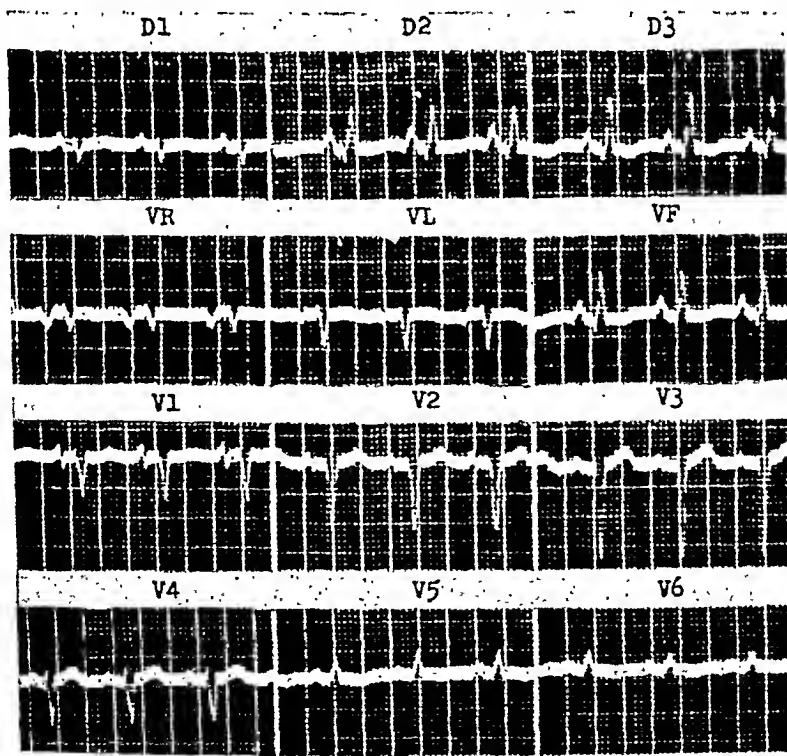


Fig. 12.—Tracing of a case of chronic cor pulmonale with cor aortale (arterial hypertension in this case). The first is diagnosed because of the P pulmonale (Leads II, III, and V_F), prominent auricular T, small precordial R waves, and diphasic ST-T (Leads II, III, and V_F). The second is strongly suggested by the absence of S in V_5 and V_6 (75 per cent of our cases without S in V_5 or V_6 were complicated by cor aortale).

SUMMARY

After the study of the electrocardiograms of fifty cases of chronic cor pulmonale, we consider that the principal diagnostic signs (see Fig. 11) are: (1) high and peaked P waves with prominent auricular T waves in Leads II, III, and V_F ; (2) negative P waves in V_L ; (3) right deviation and a decreased value of \hat{A}_{QRS} ; (4) a small ventricular gradient (frequently deviated); (5) signs of clockwise rotation of the heart (S_1 - Q_3) and backward position of its apex (S_1 , S_2 , and S_3 ; S_1 and S_2 with right deviation of \hat{A}_{QRS}); (6) diphasic (of the $- +$ type) or negative T waves in Leads III, II, and V_F ; (7) small R waves in the precordial leads; (8) deep S waves in the left precordial leads; (9) diphasic (of the $+ -$ type) or negative P waves in the right precordial leads; and (10) negative T waves in the right precordial leads.

In the differential diagnosis, we emphasize that:

(1) The delay of the intrinsic deflection in the right precordial leads is frequently attended (36 per cent) by a complication which gives rise to further strain on the right ventricle.

(2) The absence or diminished amplitude of the S wave in the left precordial leads is frequently attended (75 per cent) by a complication of the "*cor aortale*" type (Fig. 12).

(3) A QS complex, usually in the right precordial leads, a W-shaped complex, or a deep Q wave in these leads is a frequent finding (36 per cent) in chronic cor pulmonale, without clinical signs suggestive of a myocardial infarct or a dead zone.

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THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER

I. A DISCUSSION OF THE RELATIONSHIP BETWEEN A POSITIVE FAMILY HISTORY AND THE DEVELOPMENT OF RHEUMATIC FEVER IN INDIVIDUALS OF MILITARY AGE

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IN THE etiology of rheumatic fever, two fundamental mechanisms have been thought to play a role: contagion and heredity. It can hardly be doubted, in the face of actual epidemics of rheumatic fever associated with hemolytic streptococcus infection, that contagion plays a part both as an inciting factor in the development of the "initial" attack of rheumatic fever and in the exacerbation of the disease process in recurrent rheumatic fever. The fairly factual data on the infectious origin of rheumatic fever are not paralleled by similar material to support the role of heredity, although Wilson¹ has attempted to place the rôle of heredity on a firm statistical basis. She has stated: "It would seem fair to conclude from the genetic analysis of our data that the susceptibility for rheumatic fever is transmitted as a single autosomal recessive gene."^{1, p. 53} In further consideration of the hereditary mechanism, attention must necessarily be placed on the unusual age distribution of the disease, particularly its sparing of children in the early years of life. As Paul^{2, p. 96} has stated, "the infant must grow up to become rheumatic." Thus, if we are to accept the hereditary mechanism as dominant, might we not believe that it is a "susceptibility" of some obscure type that is inherited, according to Wilson's genetic hypothesis, and that the "growing up" phase represents the development of some sensitizing mechanism, that is, the development of hypersensitivity? Certain it is that most phenomena of the rheumatic state appear to have a basic allergic mechanism (Rich and Gregory³ and Akiawa⁴). Therefore, both Wilson and Paul have emphasized the need for further studies on the familial aspects of rheumatic fever.

RÉSUMÉ OF PUBLISHED DATA

The problem of familial incidence in rheumatic fever, simply stated, is the problem of separating hereditary from contact factors. Each separately, or both operating simultaneously, may play a role either in favoring the initial attack

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or in precipitating recurrent attacks. The role of heredity in rheumatic fever has been supported by the following studies and observations.

1. The similarity in susceptibility to rheumatic fever of identical and fraternal twins, (Wilson,¹ Irvine-Jones,⁵ and Kaufmann and Scheerer⁶). These analyses have been fairly uniform in showing that identical twins behave similarly genetically; that is, either both do contract rheumatic fever, or both do not. However, this is not always the case, as Paul^{2, p. 90} has pointed out.

2. Genetic analysis of rheumatic families in relation to Mendelian prediction rates in various types of gene transmission (Wilson and Schweitzer⁷).

Studies such as these form the basis for Wilson's thesis of "autosomal recessive gene transmission" to which we have referred. From a critical analysis of these studies, Paul has concluded that "some inherited relationship exists between parental rheumatic fever and that of the siblings."^{2, p. 90} More indirect evidence of the operation of heredity is obtained from Paul's consideration of the age at which second members of a rheumatic family acquire their initial attack. This occurs most often at an older age than that of the first member and is difficult, actually, almost impossible, to explain on the basis of contagion alone. It may be more logically explained on the basis of a gradually developing susceptibility of post-streptococcal origin.

The justification for the presentation of our data lies in the opportunity to inquire into the history of a large number of young adult rheumatic fever patients who have been separated for a varying period of time from the family contact. The history of the individual *following the break from family contact* affords an important method of separating hereditary influences from the factors of contagion.

SOURCE OF MATERIAL

It is the purpose of this communication to present observations on the occurrence of rheumatic fever, both initial and recurrent attacks, in relation to familial and postfamilial contacts. In contrast to the observations of Wilson and of Paul, who studied children in a relatively small number of families, this study is concerned with young adults of military age from a large number of families distributed widely over the United States. As controls, a group of tuberculous patients, a group of healthy physicians, and a group of patients in a veterans' hospital were studied.

Four separate series of patients form the basis for the present study. In each group, personal interviews were conducted by one of us, and information relative to previous rheumatic fever and family history tabulated. The composition of the four groups was as follows:

Group 1: 3,594 patients with rheumatic fever, who were interviewed over a period of twenty months in 1944 and 1945, in a naval hospital devoted almost entirely to the treatment of this disease.

Control Group 2: 519 patients of military age with tuberculosis who were seen in the same naval hospital.

Control Group 3: 254 healthy physicians who were working in a large general civilian hospital.

Control Group 4: 624 patients on the general, medical, and surgical wards of a veterans' hospital.

Groups 1 and 2 consisted of enlisted and officer personnel sent to the naval hospital for treatment. They were representative individuals from installations and ships of the United States Navy throughout the world.

RESULTS OF STUDY

The results of our observations are summarized in Tables I and II.

TABLE I. COMPARISON OF FAMILIAL INCIDENCE IN THE RHEUMATIC FEVER GROUP WITH CONTROL GROUPS

	NUMBER	PER CENT
<i>Group 1 Rheumatic Fever Patients Total 3,594</i>		
(a) Total patients with "initial" attack during military service (and therefore after separation from family)	2,819	78.4
(b) Total patients with "recurrent" attack during military service (initial attack occurred at home)	775	21.6
(c) Total patients with "initial" attack in service; family history positive	238	6.3
(d) Total patients with "recurrent" attack in service; family history positive	354	of total 9.8 of total
(e) Total patients with "initial" and "recurrent" attacks in service, family history positive; (c) plus (d)	592	16.4 cf total
(f) Percentage of patients with "initial" attacks (2,819) with family history positive (238); (c) divided by (a)		8.4
(g) Percentage of patients with "recurrent" attacks (775); with family history positive (354); (d) divided by (b)		45.6
<i>Control Group 2 Tuberculous Patients Total 519</i>		
(a) Total patients with history of previous rheumatic fever	21	4.0
(b) Total patients with rheumatic fever before break from family	9	1.7
(c) Total patients with positive history of rheumatic fever in family	9	1.7
<i>Control Group 3 Healthy Physicians Total 254</i>		
(a) Total physicians with history of previous rheumatic fever	15	5.9
(b) Total physicians who had rheumatic fever before break from family	8	3.5
(c) Total physicians with positive history of rheumatic fever in family	8	3.5
<i>Control Group 4 General Patients in a Veterans Hospital Total 624</i>		
(a) Total general patients who had had Rh. F.	40	6.4
(b) Total general patients who had Rh. F. before break from family	23	3.7
(c) Total general patients with positive history of Rh. F. in family	15	2.4

TABLE II. THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER IN THE FOUR GROUPS WHEN FAMILIAL CONTACT IS CONSIDERED ALONE

	NUMBER	PER CENT
Group 1		
Incidence of family history in patients with "initial" attacks of rheumatic fever; that is, while still in contact with the family		45.6
Total rheumatic fever patients ("initial" attack at home)	775	
Total family history positive	354	
Control Group 2		
Incidence of familial history in tuberculous patients who had had rheumatic fever while still in contact with family		42.9
Total tuberculous patients with rheumatic fever	21	
Total with family history positive	9	
Control Group 3		
Incidence of familial history in physicians who had had rheumatic fever while still in contact with family		53.3
Total physicians with rheumatic fever	15	
Total with family history positive	8	
Control Group 4		
Incidence of familial history in general patients in a veterans hospital who had had rheumatic fever while still in contact with family		37.0
Total veterans' hospital patients with rheumatic fever	40	
Total with family history positive	15	
Average familial incidence for all groups		44.7

Comment: (1) In Group 1, Table I, 16.4 per cent of all patients with rheumatic fever had a positive family background; 45.6 per cent of rheumatic fever patients with "recurrent" attacks had a positive family background. In the three control groups, patients with tuberculosis, healthy physicians, and patients in a general veterans' hospital, the incidence of a positive family history of rheumatic fever was 1.7 per cent, 3.5 per cent, and 2.4 per cent, respectively. These figures are not, to our knowledge, unlike those in previously published reports, and call attention again to the definite importance of the family in the etiology of rheumatic fever.

(2) Of the rheumatic fever patients who developed an "initial" attack after separation from the family, 8.4 per cent had a positive family background, while 91.6 per cent of these patients had no knowledge of any occurrence of the disease within the family. It would appear that the actual attack rate, as exemplified in this large group of military personnel separated from familial contact, was determined by external factors, such as environment and infection, rather than by hereditary or familial factors.

(3) Table II illustrates the familial incidence in those patients who had had rheumatic fever while still in contact with family. In these groups, the incidence of a positive family history (44.7 per cent, average) is considerably higher than the incidence (16.4 per cent, average) in the rheumatic patients of Group 1. This high incidence shows the importance of a factor or factors which increase the tendency to develop rheumatic fever while in the home. It should be noted

that these similarly high percentages were obtained by random sampling of widely separated and dissimilar control groups. It is of great importance to note that none of the patients in Control Groups 2 and 3 who had rheumatic fever at home developed later attacks. It may be assumed that the high percentage of familial incidence in those patients who developed the rheumatic state while in contact with the family was due to contact in the home, in the same way that the high percentage of patients who developed rheumatic fever without a family history was due to contact with an inciting agent in the crowded quarters of the barracks.

It is certainly not within the scope of this paper to enlarge upon the nature or modus operandi of the infectious agent or to elaborate upon the possibility of a sensitization mechanism. We believe, however, that attention should be called to the disparity between the low familial incidence in "initial" attacks (Table I, Group 1) occurring after separation from the family (6.3 per cent) and the high familial incidence in those groups (Table II) who developed the "initial" attack while in contact with the family (44.7 per cent, average for the four groups).

In the military service the vast majority of cases of rheumatic fever developed in the training camps, where crowding in barracks permitted epidemics of hemolytic streptococcus infection to occur. Undoubtedly such epidemics occurred from contact. Is it possible that those patients who developed rheumatic fever prior to military service might have done so from contact with the streptococcus in the home? One may, therefore, raise the question whether the family carries a significantly larger place in the etiology of rheumatic fever than a source of contact. Is the family different from the barracks or a training center as a locus for contact with the inciting infectious agent? The further study of the 78.4 per cent of patients in Group 1 who developed rheumatic fever after separation from the family will help to answer the problem of hereditary susceptibility versus poststreptococcal sensitivity as the cause of recurrent attacks.

CONCLUSION

1. Four groups of young adults have been interviewed. One group of rheumatic fever patients (3,594) and three groups of nonrheumatic individuals (1,397), serving as controls, formed the basis of the study.

2. Group 1 shows that approximately 78 per cent of the patients with "initial" rheumatic fever developed the disease after separation from the family. We raise the question whether this indicates some agent outside of the family as the chief factor operative in the etiology of rheumatic fever.

3. The tuberculous patients and healthy physicians who had "initial" attacks of rheumatic fever while at home did not develop secondary attacks after separation from the family.

4. It is noted in Groups 2, 3, and 4, the controls, that the individuals who developed rheumatic fever prior to separation from the family showed a similar family incidence, and that this incidence does not differ greatly from that found in the rheumatic patients studied.

5. The high familial incidence of rheumatic fever, averaging 44.7 per cent in those who developed the disease while still at home, seems to indicate that

there is some factor within the family. Is this factor a hereditary susceptibility or contact with the inciting agent in the home?

6. The great need for further data on the subject of heredity versus environment is evident.

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THE FAMILIAL INCIDENCE OF RHEUMATIC FEVER

II. A STATISTICAL STUDY OF THE FAMILIAL AND PERSONAL HISTORY OF RHEUMATIC FEVER

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A POSITIVE familial history of rheumatic fever could be of importance in determining the risk of an individual developing the disease in several conceivable ways: first, because it might indicate a fundamental and inherited familial susceptibility; second, because it might indicate some social, economic, or climatic environment which predisposes to rheumatic fever and is shared by the family; or, third, it could influence the risk because a prerequisite to rheumatic fever might be an infection which is transmitted by contact. *It would seem justifiable to assume that any fundamental and inherited susceptibility which increases the risk of developing the disease by an individual should do so not only while the individual remains at home, but also after he has left the family environment.* In order to learn whether or not this is true, we have made a study of the familial history in patients who did or did not develop rheumatic fever while still in contact with the family or after they had left their homes. The study also included an inquiry into the question of whether or not a positive personal history of the disease while still at home tended to predispose the individual to a later attack after leaving home.

METHOD OF ANALYSIS

The material studied in Part II is identical with that considered in Part I of this paper, but the material is handled on a contingency basis rather than by the comparative and descriptive method which was used in Part I. The *chi-square* test of significance was used throughout Part II.

Two populations were sampled: (A) individuals who developed rheumatic fever in the Army or Navy, most of whom were under treatment at the Corona Naval Hospital when investigated; and (B) individuals who did not develop rheumatic fever after separation from the family, these being (1) individuals under treatment for tuberculosis at the Corona Naval Hospital, (2) intern and

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resident physicians of a large civilian hospital, and (3) Army personnel on the medical and surgical wards of the Birmingham General Hospital. The total number of individuals studied was 4,991. Table I shows the number of individuals in each of the foregoing groups:

TABLE I. NUMBER OF PATIENTS STUDIED IN THE VARIOUS GROUPS

	TOTAL
Group A Developed rheumatic fever after leaving home	3,611
Group B Did not develop rheumatic fever after leaving home	
(1) Tuberculous cases at Corona Naval Hospital	519
(2) Medical and surgical patients at Birmingham General Hospital	607
(3) Intern and resident physicians at a civilian hospital	254

The question arose as to whether these individuals were likely to have been equally well informed concerning the occurrence of rheumatic fever in members of their families. It was suspected that individuals who had not had the disease themselves might be relatively uninformed in this respect in comparison with those who had developed the disease, unless the individual was himself a physician. On review of the data, this was found to be the case; nonmedical subjects who had never had the disease reported a significantly lower familial incidence than did physicians who had never had rheumatic fever. It was, therefore, necessary to exclude from this analysis of the effects of familial rheumatic fever all of those individuals who had not had the disease themselves and were not themselves physicians, the number of cases so excluded on the basis of inadequate information being 1,082. With respect to the influence of one attack of the disease upon the development of later attacks after leaving home, there was no reason to suppose that the knowledge of an earlier attack was less accurate in those who did not develop a later attack or more accurate in those who did; all 4,991 cases, therefore, were used in this analysis.

FINDINGS

In the "informed groups," as just defined, a study was made of the relationship between a positive family history of rheumatic fever and personal development of the disease while still in contact with the family. The results, in the form of a contingency table, are shown in Table II:

TABLE II. RELATIONSHIP BETWEEN FAMILY HISTORY AND PERSONAL ATTACK BEFORE LEAVING FAMILY

FAMILY HISTORY	PERSONAL HISTORY BEFORE SEPARATION FROM FAMILY	
	POSITIVE	NEGATIVE
Positive	369	258
Negative	551	2,731

These results could not possibly have been due solely to chance; there is, therefore, a definite tendency for the individual with a positive family history to develop the disease while still in contact with his family.

A study was made of the relationship between a positive family history and the personal development of the disease in the individual after separation from his family. The results, in the form of a contingency table, are shown in Table III.

TABLE III. RELATIONSHIP BETWEEN FAMILY HISTORY AND PERSONAL ATTACK AFTER LEAVING FAMILY

FAMILY HISTORY	PERSONAL HISTORY AFTER SEPARATION FROM FAMILY	
	POSITIVE	NEGATIVE
Positive	582	45
Negative	3,029	253

These results could easily have been due solely to chance; there is, therefore, no relationship between family history and the personal development of the disease after separation from the family. This same conclusion is reached when the cases are separately studied according to their own past personal histories.

From Tables II and III it is concluded that a positive family history is important only as long as the individual remains in contact with the family, and that a positive family history has no influence upon the risk of developing the disease after the individual leaves home.

It is now possible to study the role of a past personal history upon the risk of developing rheumatic fever without regard to family history. The reason for excluding the relatively "uninformed group" from such a study is now no longer present, since those who compose that group are presumed to be uninformed only in respect to the family history.

Table IV, therefore, includes all subjects studied and shows the relationship between personal past history of rheumatic fever and the later development of the disease.

TABLE IV. RELATIONSHIP BETWEEN PERSONAL PAST HISTORY OF RHEUMATIC FEVER AND THE LATER DEVELOPMENT OF THE DISEASE

PAST HISTORY OF RHEUMATIC FEVER	LATER DEVELOPMENT OF RHEUMATIC FEVER	
	YES	NO
Positive	861	59
Negative	2,750	1,321

This result could not have been due solely to chance; it is, therefore, clear that a positive personal history does tend to influence the later development of the disease.

Further study indicated that there was no significant difference in the incidence of a positive personal history between the three control groups composed of cases who did not develop rheumatic fever after separation from home; of the total 1,380 control cases, 2.9 per cent had a positive personal history. These data emphasize again the high frequency of rheumatic fever in the population, for nearly one in thirty-five of the young adults in the control groups had had this disease earlier in life.

SUMMARY

1. Three per cent of those making up the normal control groups had a personal history of rheumatic fever earlier in life.
2. An attack of rheumatic fever earlier in life tends to facilitate a later attack, but this difference is not great.
3. The occurrence of rheumatic fever in the family increases the risk of the individual developing the disease while still in contact with the family, but not after he is separated from the family. There does not, therefore, appear to be a strong and inherited susceptibility. The occurrence of multiple cases in families could be explained either on the basis of common environment or contagion. In the light of the widely accepted relationship of streptococcal infection to rheumatic fever, and the lack of agreement concerning the roles of social, economic, and geographic factors, we prefer to look on these data as indicating the dominant role of contagion in the development of rheumatic fever.

DIFFERENT MECHANISMS OF FUSION BEATS

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THE effect on the electrocardiogram of the simultaneous stimulation of a cardiac chamber by two impulses has been observed under various circumstances, and its experimental production has been used to clarify some of the fundamental problems of electrocardiography. Lewis and associates¹ arrived at an estimate of the duration of the impulse spread from the S-A node to the A-V node from the P-R interval of the beats with "transitional" auricular complexes, in a case in which the two pacemakers were competing. Wilson and Herrmann² in their experimental study of incomplete bundle branch block produced "combination complexes" by varying time relations of the normal levocardiogram and dextrocardiogram; their experiments led to the important conclusion that a delay in the passage of the impulse through one of the bundle divisions which amounts to more than three or four hundredths of a second (in the dog) will produce the same results in the electrocardiogram as complete division of one bundle branch. Furthermore, they observed the occurrence of a number of varying ventricular complexes after cutting both bundle branches, and attributed this phenomenon to the simultaneous activity of two ventricular pacemakers; they concluded that complete bundle branch block in man, associated with ventricular complexes of varying form, was usually due to bilateral bundle branch block, and was not due to a lesion of the main stem of the A-V bundle. This was later confirmed in an autopsied case reported by Don, Grant, and Camp.³ Recently, Butterworth and Poindexter,^{4,5} by using an abnormal electric conducting pathway in the dog and in the cat, produced electrocardiograms closely resembling those seen in patients with the Wolff-Parkinson-White syndrome; they concluded that the abnormal ventricular complexes were "fusion beats"^{6,7} due to the fusion within the ventricles of the sinus impulse conducted both via the usual pathway and via a faster conducting accessory pathway. It has been recognized that several mechanisms can cause fusion beats. The material presented in this paper was collected in order to illustrate the various mechanisms responsible for fusion beats as they are encountered in clinical electrocardiography.

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TABLE I. CLASSIFICATION OF FUSION BEATS

				Premature systoles (Figs. 1, A and B, and 2). Escapes in { Sinus bradycardia S-A block (Fig. 3) 2nd degree A-V block	
				Idioventricular beats { Complete A-V block (Fig. 1, C)	
				Sinus node (Figs. 4 and 5, B) Auricular ectopic focus A-V node Flutter Fibrillation (Fig. 5, A) Premature systoles (Figs. 4 and 5, A), or tachycardia with A-V dissociation (Fig. 5, B) Escape In A-V dissociation with aberrant conduction of nodal beats In A-V dissociation in Wolff-Parkinson-White syndrome (Fig. 7) Two idioventricular pacemakers in complete A-V block (Fig. 6) Ventricular premature systoles from two or more foci	
				Of sinus origin when QRS is less than 0.12 second. Wider QRS may also indicate fusion (Fig. 7) In auricular fibrillation (Fig. 5, C)	

FUSION BEATS

VARIETIES OF FUSION BEATS

A classification of fusion beats is presented in Table I. Fusion beats can be classified according to two criteria: (a) the origin of the fusing impulses, and (b) the site of the fusion. Since the fusing impulses can be of either different or identical origin, and since fusion which is reflected in the electrocardiogram can take place either in the auricles or in the ventricles, four different types of fusion beats can be distinguished.



Fig. 1.—Three examples of auricular fusion beats. A, Fusion of the retrograde impulse of a ventricular premature systole with the sinus impulse (F). After the second ventricular premature systole, no sinus P wave is inscribed nor is there any retrograde P. B, Different degrees of fusion (F) between the retrograde impulse of nodal premature systoles and sinus impulses. The P waves show transition from the deeply inverted retrograde P (first beat) to the tall upright sinus P wave. The shortened P-R of the premature beats and the fixed coupling speak for this interpretation and tend to rule out the occurrence of multiple auricular premature systoles from different foci. C, Fusion of the retrograde impulse of an idioventricular beat with the sinus P in a case of complete A-V block with preserved retrograde conduction. The P waves following the third and fourth idioventricular QRS have an intermediate contour between the retrograde and the sinus P, and they occur at a time when both the sinus P and the retrograde P can be expected.

The mechanism in each case of this and subsequent figures is illustrated in the diagram below the electrocardiogram. The conventions are those used customarily. S-A indicates the impulse spread between the sinus node and the auricles. A-V represents the spread of the impulse through the A-V junction between the auricle (A) and the ventricle (V). Sinus impulses are indicated by solid lines. Ectopic impulses by dash lines. F indicates a fusion beat. Variations in its location are represented by varying the level at which the two vertical lines meet. Block and interference are indicated by short lines at right angles to the lines representing the impulse spread.

(A) *Fusion of Impulses of Different Origin.*—

(1) *Auricular Fusion Beats:* Such fusion beats are due to the sinus impulse fusing with the retrograde impulse of an A-V nodal or idioventricular beat; the latter may be either a premature systole (Figs. 1, *A* and *B*, and 2) or an escape occurring during the ventricular pause caused by marked sinus bradycardia, S-A block (Fig. 3), or A-V block (Fig. 1, *C*). It is rare to find auricular fusion beats resulting from the fusion of the sinus impulse with that of an auricular premature systole⁸ or from fusion of two auricular premature systoles.

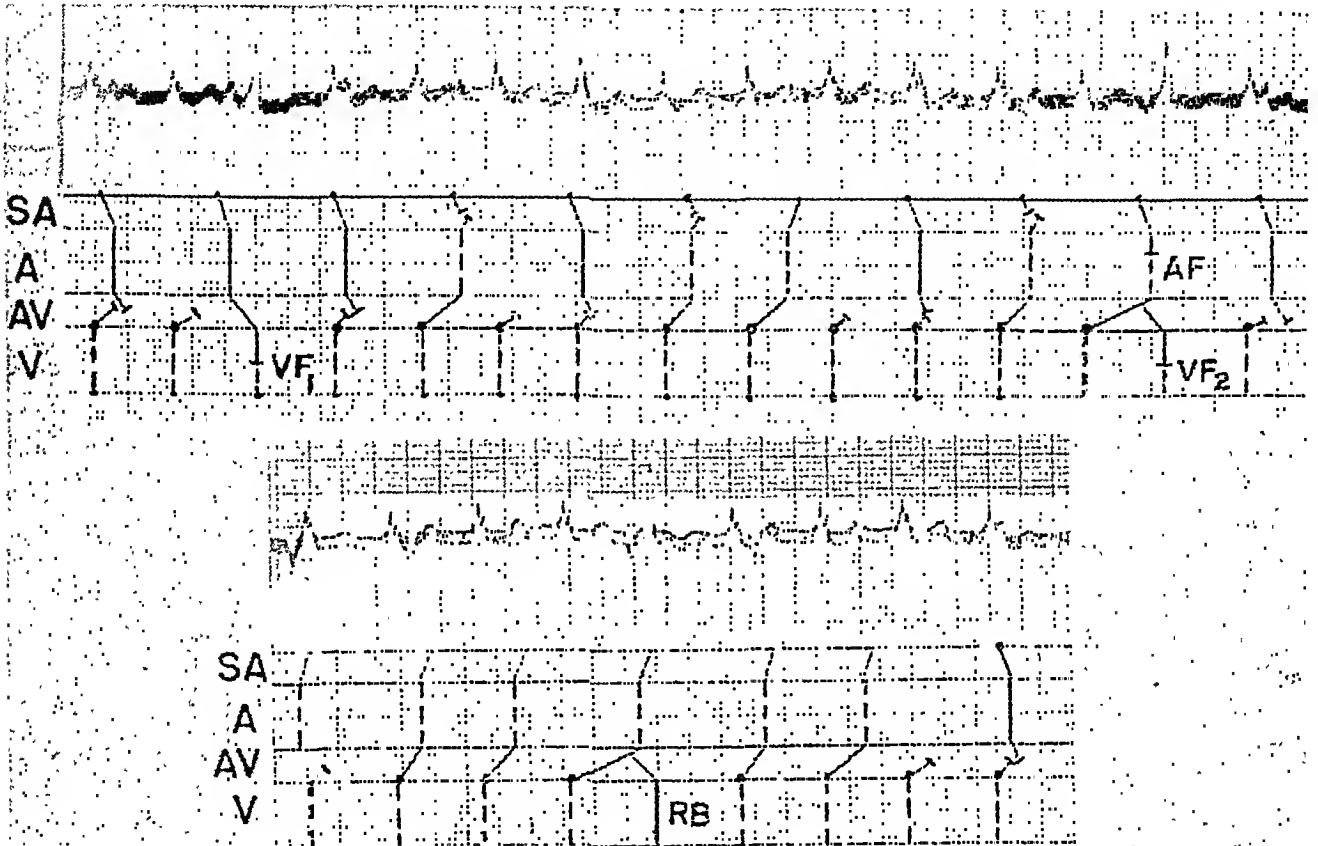


Fig. 2.—Two portions of the same record (Lead II) showing auricular and ventricular fusion beats in a case of ventricular paroxysmal tachycardia with retrograde conduction, retrograde block exhibiting the Wenckebach phenomenon, and reciprocal beats. Three types of P waves are seen: (a) upright sinus P waves, (b) deeply inverted (retrograde) P waves, and (c) a fusion P wave (AF) with an intermediate contour between (a) and (b), and occurring at the time when a sinus P wave was expected. Note that in the second strip only one sinus P is seen, due to the fact that the sinus rate is slower than in the first strip and most retrograde impulses reach and discharge the sinus pacemaker.

In addition, three types of ventricular complexes are seen: (a) A broad, notched QRS of idioventricular origin occurring at a rate of about 120 per minute and with slightly varying contour due to the superimposition of sinus P waves. (b) One beat has a normal QRS duration preceded by a retrograde P and representing a reciprocal beat (RB). (The forward conduction of this beat and of a later such beat is represented by solid lines.) (c) Two ventricular complexes show intermediate contour between (a) and (b). The first one (VF₁) is the result of fusion of impulses from the sinus and from the idioventricular pacemakers. The second one (VF₂) results from the fusion of two impulses of identical origin; the reciprocal impulse invades the ventricle simultaneously with the next idioventricular impulse. Note that this latter follows an auricular fusion beat, thus suggesting that re-entry occurs below the auricles.

The preceding explanation was arrived at and is substantiated by the analysis of several long strips obtained on the same patient.

Conventions as in Fig. 1.

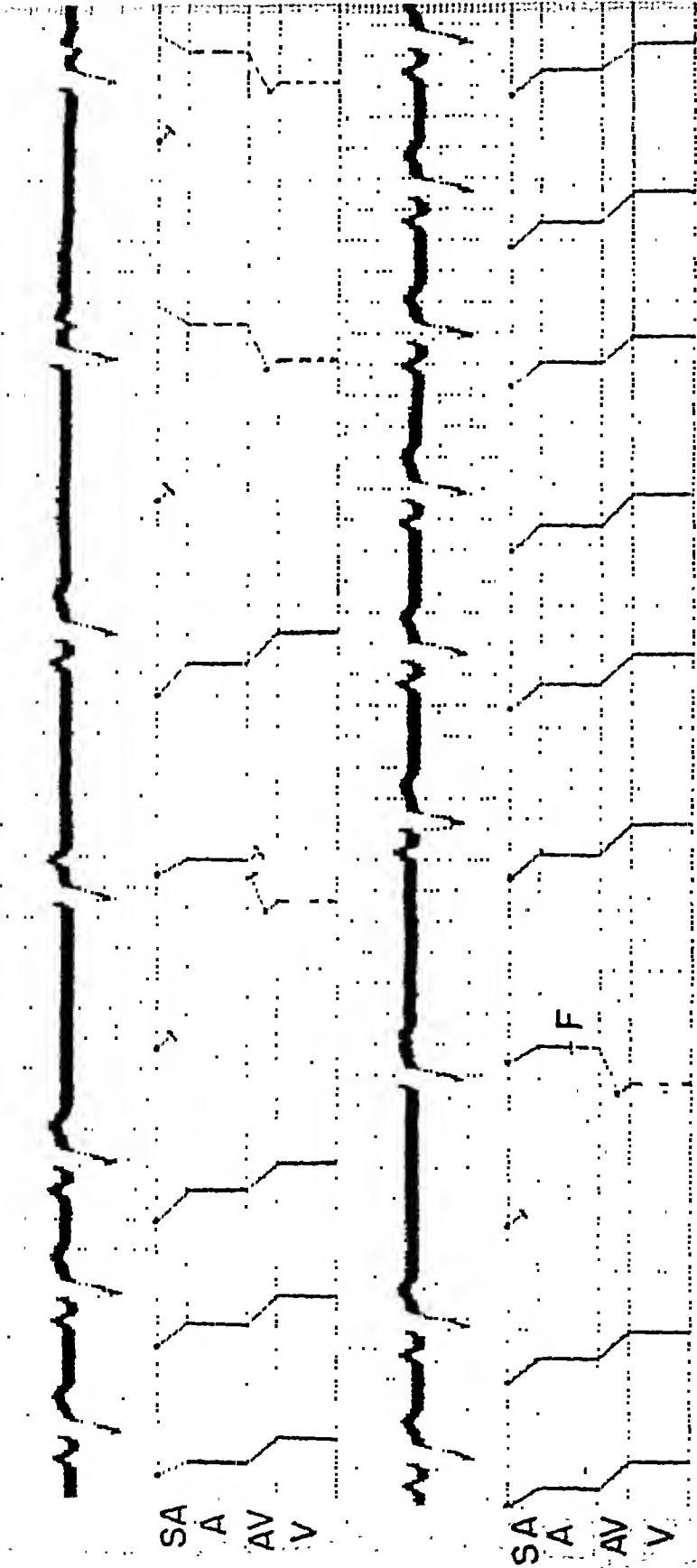


Fig. 3.—Two portions of the same Lead II showing an auricular fusion beat occurring in a case of S-A block with nodal escapes followed by retrograde P waves. The fusion beat (F), shown in the lower strip, is intermediate in contour between the retrograde and the sinus P. Note that the interval between the fourth and fifth sinus P in the upper strip is almost identical with the interval between the fusion beat and the following sinus P, confirming that a sinus P was inscribed during F. The R-P interval of the fusion P is similar to that of the last two beats in the upper strip. Conventions as in Fig. 1.

(2) *Ventricular Fusion Beats*: Such fusion beats result from fusion of a supraventricular impulse with a ventricular premature systole or a ventricular escape; the supraventricular impulse may be sinus (Figs. 2, 4, and 5, *B*), auricular, or A-V nodal in origin, or it may be the impulse of auricular fibrillation (Fig. 5*A*) or auricular flutter. Fusion beats with varying time relations between the supraventricular impulse and the premature impulse of a single ectopic focus

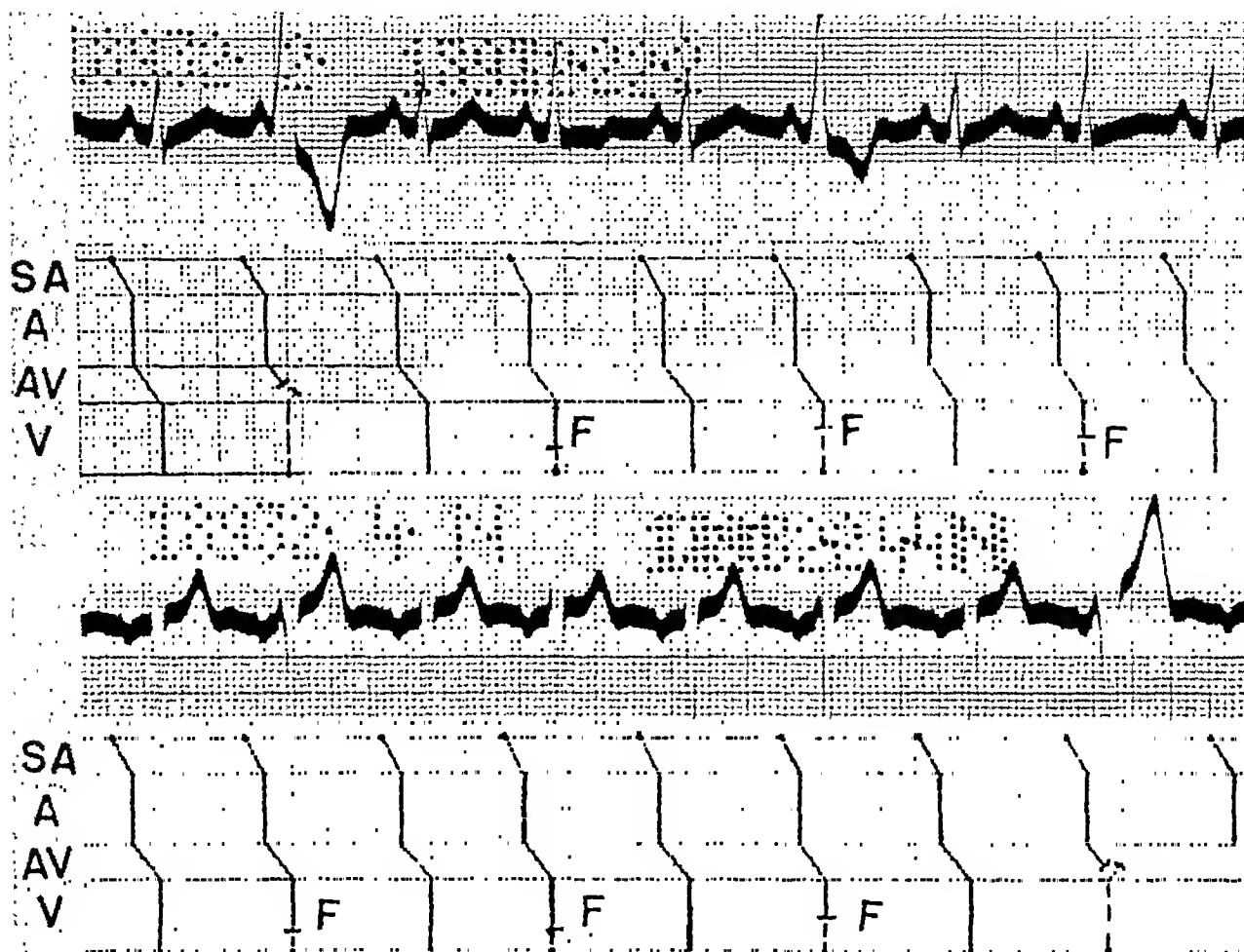


Fig. 4.—Leads II and CF_2 of the same patient showing fusion (*F*) of sinus impulses and late ventricular premature systoles in a case of parasystole. The difference in contour of the several ventricular fusion beats indicates variations in the fusion. It is apparent that the closer the P-R approaches the sinus P-R, the larger is the share of the ventricles controlled by the sinus impulse, as evidenced by its greater approximation to the sinus contour.

Conventions as in Fig. 1.

may lead to the erroneous diagnosis of premature systoles from multiple foci if the mechanism of fusion is not recognized; this is especially likely to occur in cases with auricular fibrillation (Fig. 5, *A*). In cases of A-V dissociation and aberrant conduction of the nodal beats, ventricular complexes can be found intermediate in contour between that of the sinus and nodal beats which occur at a time when fusion of the two impulses is to be expected. In cases of Wolff-Parkinson-White syndrome presenting A-V nodal escapes, supraventricular impulses conducted via the accessory pathway may fuse with the nodal impulses conducted via bundle of His and give rise to a transitional form of the ventricular

complex (Fig. 7) (Rosenbaum and associates,⁹ and Ohnell¹⁰). This is true both for cases with sinus rhythm and for those with auricular fibrillation; it could also occur in the presence of nodal premature systoles. Finally, ventricular fusion beats occur as a result of simultaneous stimulation by two idioventricular impulses, as seen in cases of complete A-V block with two competing idioventricular pacemakers (Fig. 6). Similar fusion may occur in the presence of ventricular premature systoles from multiple foci; however, its recognition is difficult unless both are parasystolic in origin.

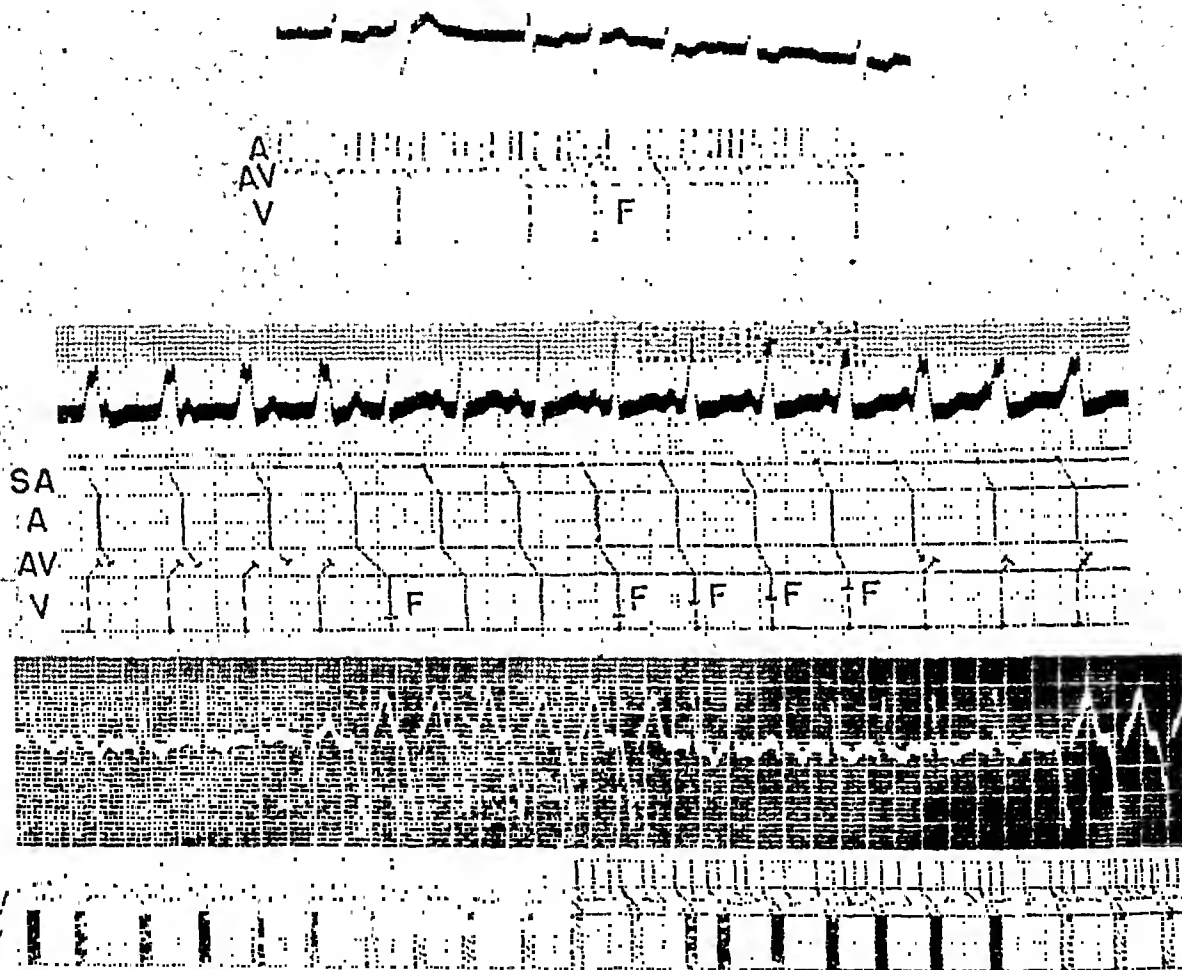


Fig. 5.—A, Ventricular fusion beat in a case of auricular fibrillation. Fusion occurs between the supraventricular impulse and a ventricular premature systole. This is evidenced by the identical coupling of the ventricular premature systole and the fusion beat as well as by the intermediate contour of the latter. B, Varying location of fusion in a case of ventricular paroxysmal tachycardia with A-V dissociation. The gradual transition in contour of the ventricular complexes is explained by the small difference in rate between the slower sinus and the faster ventricular pacemaker. (This record was obtained on the patient shown in Fig. 2, on an occasion when no retrograde conduction from the ventricular pacemaker was present.) C, Ventricular fusion beats in a case of Wolff-Parkinson-White syndrome with auricular fibrillation. The wide QRS complexes are identical with those found during sinus rhythm showing short P-R and prolonged QRS (not illustrated). The fifth and sixth beats show a gradual transition from the narrow to the wide QRS, indicating the simultaneous invasion of the ventricles by a supraventricular impulse over both the bundle of His and accessory pathway. The difference in contour between these beats indicates an increasing share of the control of the ventricles by way of the accessory bundle.

Conventions as in Fig. 1, but in C, the solid rectangles indicate stimulation of the ventricles via the bundle of His. The shaded portion represents stimulation via an accessory bundle. The spread over the two pathways is indicated by the double oblique lines in A-V.

(B) *Fusion of Impulses of Identical Origin.*—Such fusion beats could occur in A-V block with re-entry and when the impulse spreads along a double pathway.

(1) *Auricular Fusion Beats:* No such fusion beats were encountered in our material; however, in a case reported in the literature,¹¹ the conditions which could give rise to such fusion beats were present. The case presents the unique picture of sinus rhythm with 2:1 A-V block and re-entry of the sinus impulse

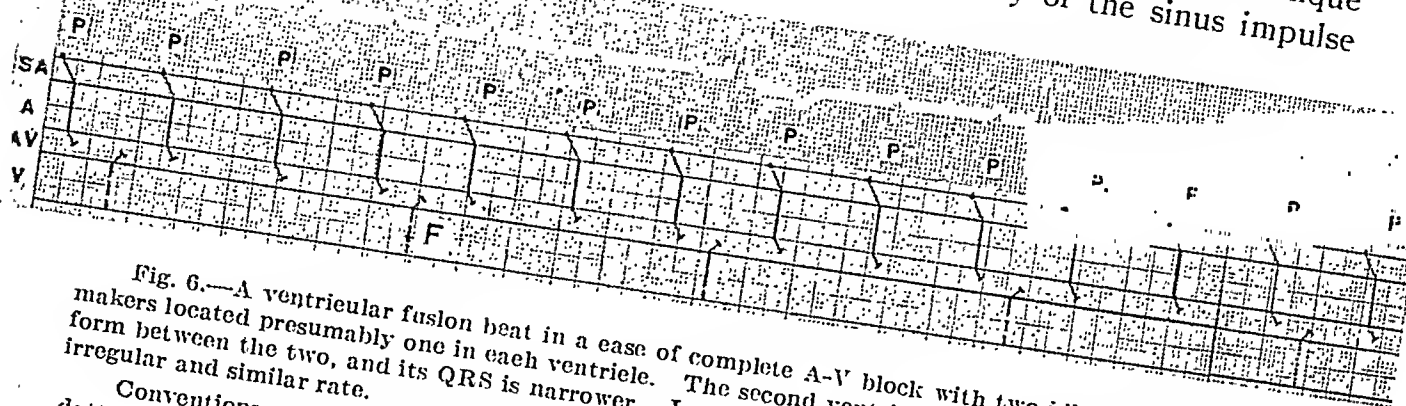


Fig. 6.—A ventricular fusion beat in a case of complete A-V block with two idioventricular pacemakers located presumably one in each ventricle. The second ventricular beat shows an intermediate form between the two, and its QRS is narrower. Longer records show that both pacemakers have an irregular and similar rate.

Conventions as in Fig. 1, except that the second idioventricular pacemaker is represented by a dotted line.

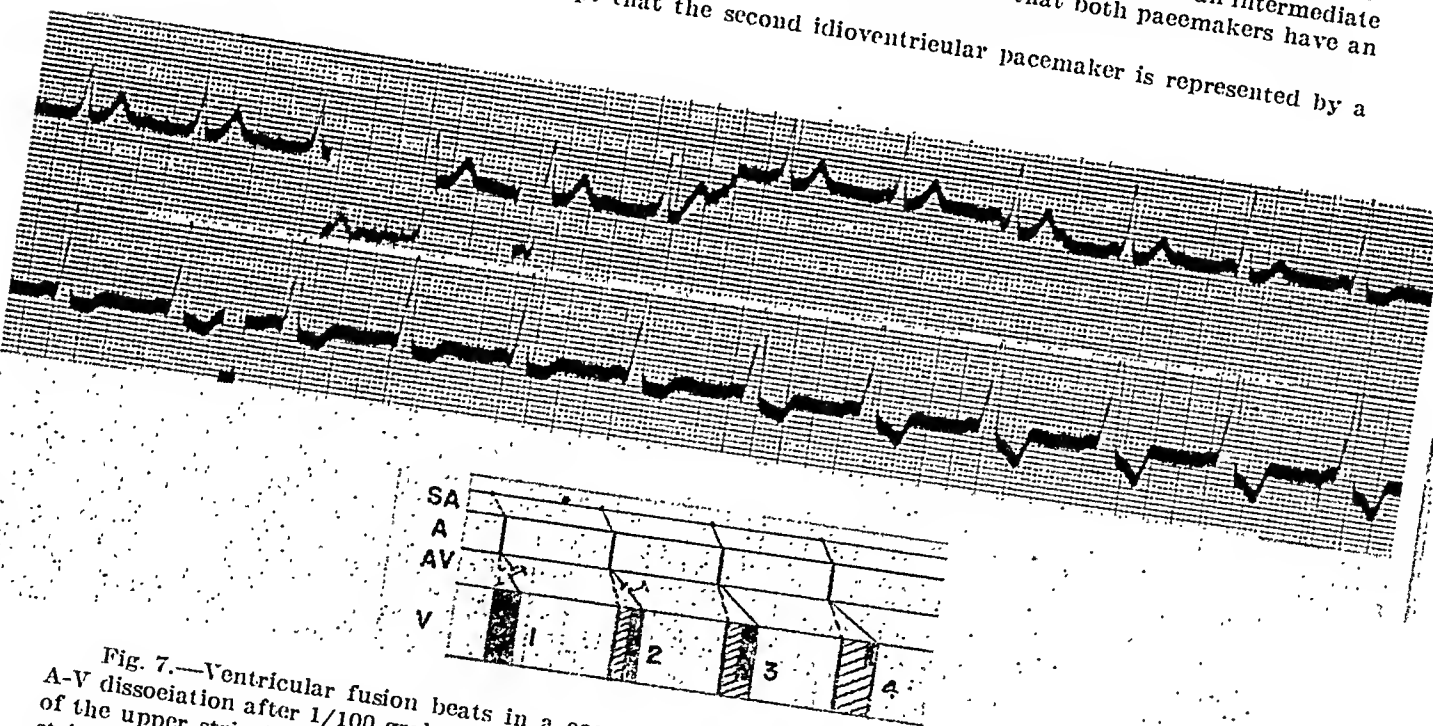


Fig. 7.—Ventricular fusion beats in a case of Wolff-Parkinson-White syndrome with transitory A-V dissociation after 1/100 grain of atropine sulfate intravenously. Continuous record, the last beat of the upper strip is repeated at the beginning of the lower strip. The first four beats of the upper strip show A-V nodal rhythm with QRS of normal duration (Diagram 1). Starting with the fifth beat a P wave appears in front of QRS and the P-R lengthens gradually to 0.10 second, QRS gradually becomes wider with slurring of its initial portion, and R becomes taller, S-T becomes depressed, and T inverted (Diagram 2). It is possible that the contour changes in the second strip are no longer associated with escape of the nodal pacemaker. The whole heart may now be under the control of the S-A node, partly via the accessory bundle and partly via the bundle of His. However, the site of fusion of the impulse conducted over the normal pathway with that conducted along the accessory bundle varies as the effect of atropine on the conduction through the A-V node disappears (Diagrams 3 and 4). Nevertheless, it cannot be ruled out that the transitional contour in the first portion of the lower strip still reflects the interplay of the two pacemakers.

Conventions as in Fig. 5, C.

giving rise to reciprocal auricular beats; fusion in the auricles of the reciprocal impulse with the next sinus impulse would result in a fusion beat.

(2) *Ventricular Fusion Beats*: Such beats occur in cases of ventricular rhythm associated with reciprocal beats, the fusion being between the reciprocal and the next automatic beat (Fig. 2). In A-V nodal rhythm with reciprocal beats, such fusion beats can be diagnosed only when the reciprocal or nodal beat shows aberrant conduction. Another type of ventricular fusion beat is due to spread of the supraventricular impulse along both the normal A-V bundle and an accessory A-V bundle, as present in cases with the Wolff-Parkinson-White syndrome. Whether all the beats in such cases with sinus rhythm, short P-R, and prolonged QRS are actually fusion beats cannot be answered. Uniformity and lack of transitional complexes would seem to indicate that the difference of the conduction times of the two pathways is of such duration that the impulse conducted through the accessory bundle stimulates both ventricles before the impulse can reach the ventricles via the slower A-V conducting path. However, the fact that the sum of the P-R and QRS intervals remains constant in records showing both normal P-R with normal QRS and shortened P-R with prolonged QRS suggests that the last portion of the wide QRS may be due to stimulation by the impulse conducted along the normal pathway. This is undoubtedly true in the cases of Wolff-Parkinson-White syndrome without abnormal QRS prolongation but with the typical notching of the first portion of QRS (Fox,¹² Öhnell,¹⁰ and Katz, Langendorf, Mintz, and Malinow¹³); whenever the value representing the difference in A-V conduction time along the two pathways is within a critical range, any procedure (like carotid sinus pressure) or medication (like atropine) that changes vagal tone and with it the conduction delay of the impulse spreading normally through the A-V node will shift the site of fusion and influence the duration of QRS and the contour of its second portion (Fig. 7). In the combination of auricular fibrillation and the Wolff-Parkinson-White syndrome (Langendorf¹⁴) ventricular fusion beats are to be expected with varying time relations between the supraventricular impulses conducted along the two pathways: this actually can be demonstrated (Fig. 5, C).

Most fusion beats are premature. In the commonest form of fusion, a ventricular premature impulse fuses with a sinus impulse, thus abbreviating the P-R interval. This shortening may amount to as much as 0.06 second in the human heart (Ashman and Hull¹⁵), indicating that the conduction from the ectopic focus to the bifurcation of the common bundle may require as much as 0.06 second. As was demonstrated in animal experiments,² such shortening of the P-R of a fusion beat can be absent in a case of bundle branch block where the sinus impulse fuses with an impulse originating in the ventricle affected by the bundle branch block.

SUMMARY

(1) A review is presented of the contributions to the understanding of the normal and abnormal spread of the cardiac impulse, which have been revealed by the study of fusion beats (transitional complexes, combination complexes) in the electrocardiogram.

(2) A classification of fusion beats is given, based on two criteria: origin of the fusing impulses and site of fusion.

(3) The various mechanisms reflected in the electrocardiogram exhibiting fusion beats are discussed and illustrated.

(4) A case of Wolff-Parkinson-White syndrome with auricular fibrillation, showing complexes with a transitional contour (fusion beats), is presented as new evidence to demonstrate the functioning of both the normal, and an accessory, pathway in the Wolff-Parkinson-White syndrome.

We are indebted to Dr. L. N. Katz for his valuable suggestions.

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GLOSSOPHARYNGEAL NEURALGIA: A CAUSE OF CARDIAC ARREST

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GLOSSOPHARYNGEAL tic douloureux or neuralgia is a comparatively rare but well-recognized syndrome. In respect to the stabbing paroxysmal nature of the pain and its relation to specific trigger zones, it is exactly comparable to the commoner trigeminal tic douloureux. In neurosurgical clinics the two types of neuralgia occur in a ratio of about one to forty.

The significance of cardiac arrest and syncope associated with glossopharyngeal neuralgia was first emphasized by Riley and associates,¹ in a brief report of two cases in 1942. This report called attention to the afferent pathway of the carotid sinus reflex through the glossopharyngeal nerve and suggested the correlation of the simultaneous neuralgia and excessive stimuli to the sinus reflex. Neither of the two cases was reported to have been subjected to operation. Since then, no other reports of similar cases have come to light in medical literature. However, one of us (Ray) had the opportunity of examining such a case with Dr. Jefferson Browder in 1943 and this patient was relieved of all symptoms by intracranial section of the glossopharyngeal nerve.

Because of the importance of further establishing the authenticity of the syndrome and calling wider attention to the importance of its recognition, there is justification for reporting another comparable case.

CASE REPORT

History.—E. L., a 49-year-old Parisian man, was admitted to the New York Hospital in June, 1946, complaining of recurring severe pain in the left side of the base of the tongue, pharynx, and neck, accompanied by fainting. He had first experienced the pain three years before when he suffered from an infection in the left tonsillar region said to have been a peritonsillar abscess. As soon as the infection had subsided a tonsillectomy was performed and the initial pain subsided after several weeks, but every few months, thereafter, he was troubled by stabs of pain in the left tonsillar region. In March, 1946, with a recurrence of pain, another operation for removal of tonsillar tissue failed to provide relief. Instead, the pain increased and for two weeks prior to admission to the hospital, it had been so severe that the patient was confined to bed. Only moderate relief had been obtained from the regular administration of morphine.

The pain was of an intense piercing quality, beginning in the base of the tongue and tonsillar region on the left side and spreading deeply in the neck just below and behind the angle of the jaw, thence deeply into the ear on the same side. A rapid succession of lightninglike stabs would continue for five to forty-five seconds, then subside as suddenly as they had appeared. Paroxysms

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recurred every several minutes during waking hours, the longest period of freedom being about ten minutes. The pain was induced by swallowing and talking so that he ate and drank very little and conversed by signs and writing.

In the more severe attacks, he felt faint and sometimes lost consciousness. Since he was under the impression that he had a "weak heart" as a result of having been exposed to gas in World War I, he feared that his heart might be failing and that death was impending.

Examination.—The general physical examination revealed nothing remarkable except for moderate obesity and dehydration. The tongue, tonsillar fossae, and pharynx were normal in appearance, the neck contained no masses, and otoscopic examination was negative. The cardiac sounds, rhythm, and size, as well as the electrocardiogram, were normal. However, the cardiac rate varied between 16 and 90 beats per minute and averaged about 65. The blood pressure averaged 90/60. The temperature and respiratory rates were normal. Urinalysis, blood counts, and blood Wassermann were all negative.

Description of Attacks.—Many attacks were observed and, with all of those in which the pain was more than a fleeting stab, there was simultaneous slowing of the pulse rate for a few seconds. With the more intense and longer lasting paroxysms, there occurred asystole for several seconds followed by bradycardia and by a fall in systolic blood pressure of 25 to 30 mm. Hg for the duration of the pain.

In the more severe attacks in which there was cardiac arrest and fall in blood pressure, the patient would become pale, lose visual fixation, show signs of confusion, and, occasionally, of complete syncope. Recovery from syncope was simultaneous with the return of normal cardiac rate and rhythm and with cessation of pain.

Electrocardiographic Record During an Attack.—During a control record (Fig. 1, A) the rate was 58 per minute. The patient was then induced to take a single swallow of cold water while Lead II of the electrocardiogram was being taken. This was followed immediately by the usual pain and dizziness. The electrocardiogram showed marked slowing of the heart rate with sinus bradycardia (16 per minute), then asystole for 3.8 seconds (Fig. 1, B). At the end of this interval there was ventricular escape, followed by retrograde conduction with an auricular premature contraction and then another ventricular escape, after which there was reversion to normal rhythm. The return to normal rhythm and a more rapid rate, 50 per minute, was accompanied by recovery of the patient from dizziness.

Cocainization of the posterior portion of the tongue and the pharynx diminished the degree of the pain but did not abolish it. Pressure on the neck over the region of the left carotid sinus induced the pain and was so poorly tolerated that it was not possible to determine the sensitivity of the left carotid sinus by pressure. Pressure over the right carotid sinus was painless and unaccompanied by any alteration in cardiac rate or blood pressure. Unfortunately, the extreme discomfort and apprehension of the patient prevented the employment of other tests which would have been instructive but unnecessary.

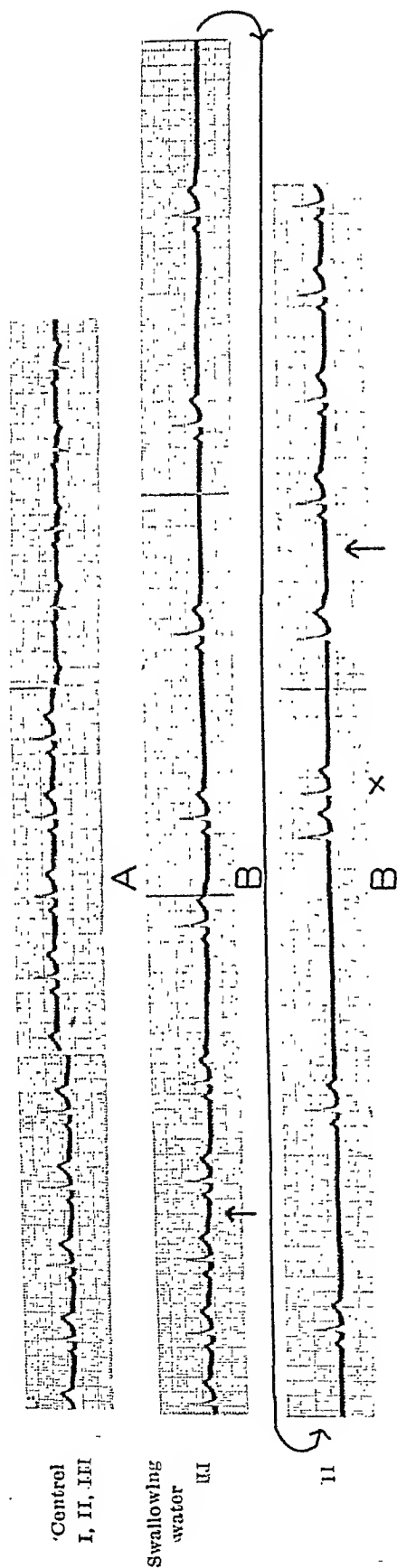
The *diagnosis* was left glossopharyngeal tic douloureux associated with an increased carotid sinus reflex.

Operation.—Intratracheal ether anesthesia was administered and a left suboccipital craniotomy performed. The left cerebellar hemisphere was uncovered and retracted medially to expose the region of the jugular foramen. The glossopharyngeal nerve was isolated from the adjacent vagus nerve and divided. The blood pressure, up to the time of dividing the nerve, had been steadily 130/85 but immediately following the division, the pressure rose precipitously to 190/115; the cardiac rate at the same time increased from 80 to 105.

Postoperative Course.—On the awakening of the patient from the anesthetic, the former pain was gone and has not returned (six months' follow-up). Recovery from the operation was prompt and uncomplicated so that he was able to leave the hospital in ten days.

Within six hours after operation the blood pressure and cardiac rate had returned to the approximate levels where they remained thereafter (blood pressure 140/80, and cardiac rate, 80).

BEFORE OPERATION



3 DAYS AFTER SECTION LEFT 9TH NERVE INTRACRANIALY

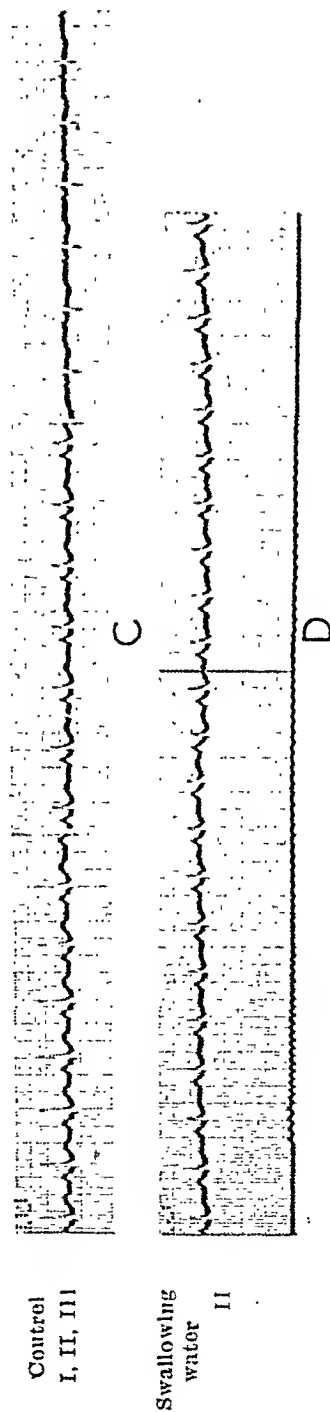


Fig. 1.—A and B show electrocardiographic observations made before section of the left ninth nerve intracranially. A shows the three standard leads of the patient's electrocardiogram as a control taken on June 21, 1946. B shows a long strip of the electrocardiogram taken immediately after A to show the effect of taking a swallow of water. The first arrow indicates the time at which the patient swallowed and the second one when he finished. There was marked slowing of the heart with sinus bradycardia following by asystole for 3.8 seconds, with ventricular escape the beat before X. This was followed by retrograde conduction with a premature contraction (X) and then another ventricular escape, after which there was return to normal rhythm when swallowing had been completed. Swallowing was associated with pain, and asystole with dizziness. C and D show electrocardiographic observations which were made three days after the left ninth nerve had been sectioned intracranially on June 21, 1946. C shows the three standard leads taken on June 24, 1946, and serve as a control. D shows Lead II of the electrocardiogram made immediately after C to illustrate the effect of swallowing. The signal at the bottom indicates when swallowing started and ended. There was no change in heart rate.

There was anesthesia of the base of the tongue, palate, and pharynx on the left in the region supplied by the glossopharyngeal nerve. The patient was unaware of this sensory loss. Pressure over the carotid sinus caused no symptoms and no alteration in blood pressure or cardiac rhythm. The form of the postoperative electrocardiogram was normal, though by comparison with the preoperative electrocardiogram there were minor changes compatible with the differences in the preoperative and postoperative blood pressures. The rate was more rapid, 87 per minute (Fig. 1, *C*). Three days after section of the left ninth nerve intracranially, swallowing was not accompanied by any change in the heart rate (Fig. 1, *D*) and he experienced no symptoms.

DISCUSSION

The nature and distribution of the pain in this patient leaves no doubt that the condition was glossopharyngeal neuralgia. It is not possible to evaluate the role of the reported quinsy that preceded the onset of the pain, but the history of tonsillar inflammation is obtained in an impressive number of those who develop glossopharyngeal neuralgia. It may be that some have had unrecognized herpes zoster of the ninth nerve but more important, perhaps, is the observation that tonsillectomy is of no aid in controlling the pain and, as in this case, cocainization of the glossopharyngeal areas supplied by the nerve cannot be expected always to abolish the pain even temporarily.

It was impossible to test the sensitivity of the left carotid sinus by pressure without inducing the pain and its accompanying alteration in cardiovascular functions. However, the absence of a hypersensitive right carotid sinus and of generalized vascular disease so commonly seen in patients with carotid sinus syncope suggests that the left carotid sinus was not hypersensitive. Thus, the cardiac arrest and fall in blood pressure may be assumed to have resulted somehow from overactivation of the afferent carotid sinus impulses traversing the glossopharyngeal nerve by a barrage of pain impulses traversing the same nerve. In some patients with hypersensitive carotid sinus reflex, there exists a dull pain which has the quality of carotidynia and both conditions appear to result from sclerotic alterations of the arterial walls; this condition is not comparable to the syndrome under discussion.

The cardiac rate and blood pressure are controlled in part by autonomic centers in the medulla whose tone is regulated by numerous afferent impulses from the body, the most important of which, perhaps, are those from the carotid sinuses. The complete afferent pathway of impulses from the carotid sinuses in man is not fully known. However, the pressure component of the reflex is mediated wholly by the glossopharyngeal nerve, as evidenced by the fact that intracranial division of this nerve abolishes all effects of digital compression of the carotid sinus in patients known to have a hypersensitive sinus.² The temporary rise in blood pressure and cardiac rate after division of the glossopharyngeal nerve intracranially is due to interruption of afferent carotid sinus impulses which exert an inhibitory effect on central autonomic centers.

In patients with the hypersensitive carotid sinus syndrome of the "vagal type," in which there is cardiac arrest and resulting fall in blood pressure, atropinization will abolish the effects of compression of the sensitive sinus. In this patient it is likely that atropinization would have done away with the cardiac

arrest and its associated fall in blood pressure and syncope, though it could hardly have been expected to alter the pain. The test was not used because of the patient's impatience with any delay in the operation to relieve his pain. Atropinization would undoubtedly be useful in excluding the cardiac effects of the syndrome during the period before a delayed operation. It would also have been interesting to observe the effects of procainization of the carotid sinus on the side of the pain, though there may possibly have been no effect.

CONCLUSIONS

1. Glossopharyngeal neuralgia may be accompanied by cardiac arrest with syncope.
2. This effect is mediated through the carotid sinus reflex mechanism.
3. Section of the ninth nerve intracranially on the affected side affords relief from the neuralgia and abolishes the episodes of cardiac arrest with syncope.

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THE DIMINISHED EFFICIENCY AND ALTERED DYNAMICS OF RESPIRATION IN EXPERIMENTAL PULMONARY CONGESTION

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INTRODUCTION

QUANTITATIVE measurements of the relative efficiency of respiration in the normal lung, as contrasted with the congested lung, have not been made in the intact experimental animal. In 1934 Christie and Meakins,¹ utilizing simultaneous determinations of dynamic intrapleural pressure and of tidal exchange in patients with congestive heart failure, demonstrated a marked decrease in pulmonary distensibility. With appropriate treatment, distensibility was found to increase as the patient improved. In the present study, an approach similar to that of these authors has been used, and studies of the efficiency of respiration have been made on normal dogs at rest and during hyperpnea (produced by the inhalation of carbon dioxide) and contrasted with the relative efficiency of respiration after pulmonary congestion induced by rapid venous infusion. With this approach, a quantitative comparison of the work necessary to achieve a given amount of tidal exchange has been possible in an animal with normal lungs and in the same animal after severe pulmonary congestion. From measurements of tidal exchange, ventilation, and intrapleural pressure fluctuations, a representation of the dynamic changes in these factors during progressive pulmonary congestion has been obtained.

PROCEDURE

Dogs were anesthetized by sodium pentobarbital (.0264 Gm. per kilogram of body weight) administered intravenously. A tracheal cannula was inserted and connected with a Benedict-Roth type spirometer, the calibrated movements of which were recorded by a pointer upon smoked paper, providing a measure of tidal exchange. Ventilation per minute was obtained by multiplying the average tidal exchange by the respiratory rate. Surface area was calculated from the Meeh-Rubner formula,² and the tidal exchange (in cubic centimeters) and ventilation (in liters per minute) were expressed per square meter of surface area. Intrapleural pressures were measured by inserting the tips of small rubber catheters (provided with lateral apertures) about three-eighths of an inch into the pleural space, by means of a small hemostat. A previously placed purse-string suture was immediately drawn airtight about the catheter. A water manometer with conduction tubing of 5 mm. bore was utilized to measure variations in intrapleural pressure. The suitability of such an instrument for recording quantitative measurements of intrapleural pressure has been shown by Christie and McIntosh.²²

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The spirometer was filled with (1) 100 per cent oxygen for experiments at rest and during congestion; and (2) with a mixture of 5 per cent carbon dioxide and 95 per cent oxygen to determine the effect of carbon dioxide. Before the administration of carbon dioxide the soda lime was removed from the spirometer, so that rebreathing caused a progressive increase in the carbon dioxide content of the inspired air, producing a maximal degree of stimulation. Venous pressures were measured from the external jugular vein (using a small amount of heparin in the manometer) with the animal's back (supine position) as a reference point. Pulmonary congestion was produced by the intravenous administration of (a) 0.9 per cent sodium chloride solution; (b) solutions containing 5 Gm. of sodium bicarbonate plus 5.55 Gm. of sodium chloride per liter; and (c) solutions containing 1.25 Gm. of sodium bicarbonate plus 7.30 Gm. of sodium chloride per liter. The rates of fluid administration varied in different animals from 5.0 to 30.0 c.c. per kilo per minute. The total amount of fluid administered varied between 2.0 and 4.0 liters per animal. Nineteen dogs were utilized. The pH of the blood was determined by means of the Coleman electrometer, using a glass electrode. Oxygen content and capacity of whole blood and the carbon dioxide content of serum were determined by the methods of Van Slyke and Neill,² carbon dioxide tension being calculated by using the Henderson-Hasselbach equation.

RESULTS

Effects of Rapid Venous Infusion.—The rapid infusion produced abrupt increases in venous pressure, which eventually rose to 500 mm. of saline or above (Table I) in most animals. Observation of the exposed cervical veins revealed that they became markedly distended during the first few minutes of the administration of fluid. The respiratory rate rose moderately, and participation of the accessory muscles of respiration, especially of the expiratory group, became progressively more marked during each experiment. In most animals the respiratory rate slowed somewhat as pulmonary congestion became very severe, and respiration became very labored. If the infusion was continued when this state was reached the animals expired very shortly. Each animal was examined after death and the lungs were universally found to be heavy, reddened, and leathery, and fluid was expressed profusely from the congested cut surface of the lungs. The liver was found to be large, reddened, and the cut surface revealed evidence of marked congestion. The heart was usually slightly dilated.

TABLE I. JUGULAR VENOUS PRESSURES (IN MM. H₂O).

DOG NO.	BEFORE INFUSION	DURING MAXIMUM PULMONAR CONGESTION
20	140	585
21	100	600
22	66	615
25	119	560
26	95	235+
27	160	510
28	85	540
30	84	540
31	105	485
32	100	520
33	87	560
34	160	450
35	85	500
36	90	600

Alterations in Intrapleural Pressure.—The maximum intrapleural pressure during expiration, before the administration of fluid or carbon dioxide, was found to be negative in eighteen of the nineteen animals (Table II), usually varying from -1.0 to -4.6 cm. of water. In the remaining animal the expiratory intrapleural pressure was at the atmospheric level, but in no instance was the expiratory intrapleural pressure at rest above atmospheric pressure. During inspiration the total intrapleural pressure fluctuations during quiet breathing in the different animals, with a few exceptions, ranged between -4.0 and -10.0 cm. of water. After the inhalation of the carbon dioxide-oxygen mixture the total intrapleural pressure fluctuations increased markedly in each animal (Table II), usually remaining below atmospheric pressure. In only three of the eight animals given carbon dioxide did the expiratory intrapleural pressure rise above the atmospheric level.

By contrast with the resting state, and with most of the experiments in which respiration was stimulated by carbon dioxide, the expiratory intrapleural pressure rose well above atmospheric pressure in every animal in which pulmonary congestion was produced (Table II and Fig. 1). In seventeen of the nineteen animals

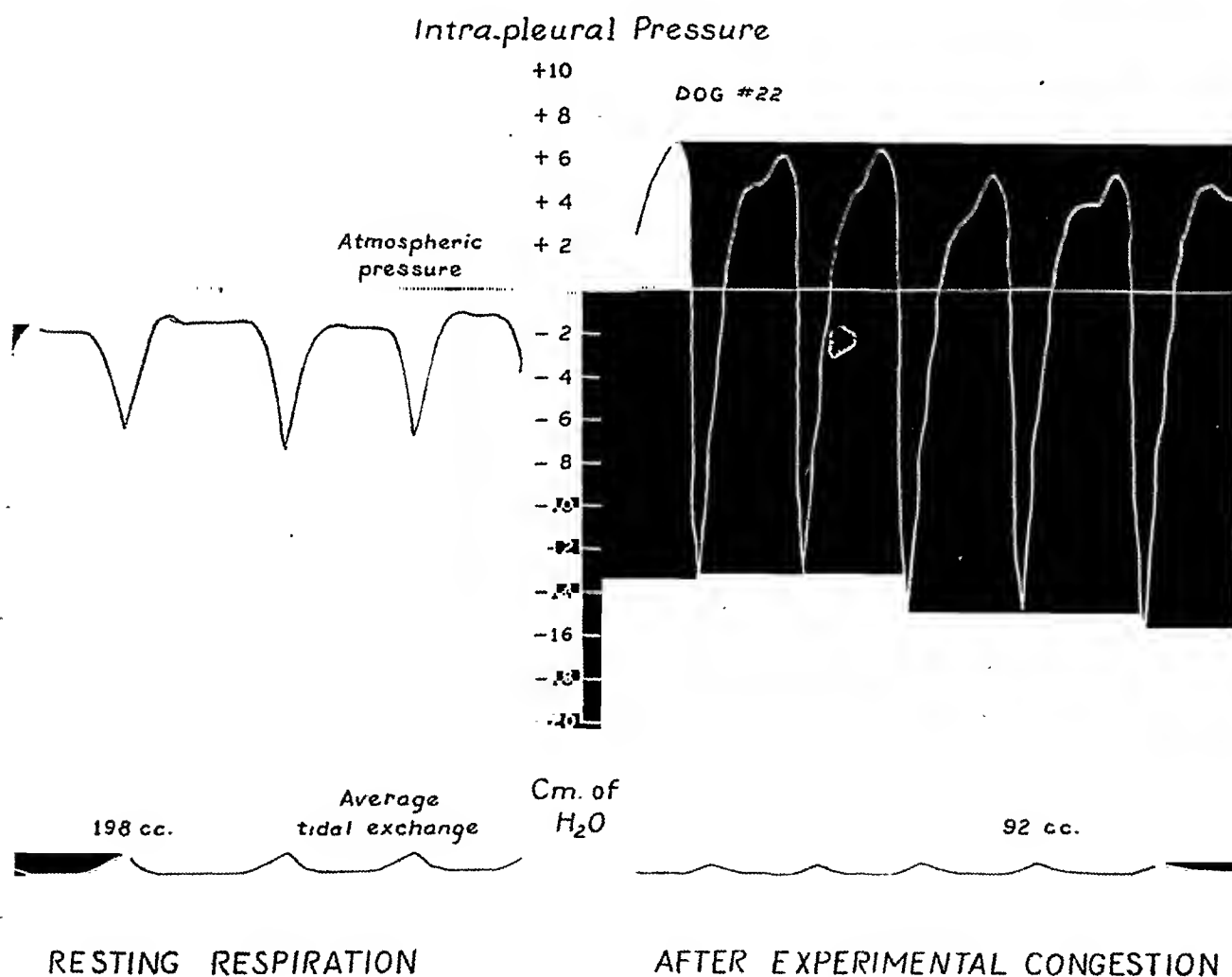


Fig. 1.—Effects of rapid intravenous infusion upon intrapleural pressure and tidal exchange (expressed per square meter of surface area).

TABLE II. INTRAPLEURAL PRESSURES (IN CM. H₂O)

DOG	QUIET BREATHING			AFTER CO ₂ INHALATION			DURING MAXIMAL PULMONARY CONGESTION		
	INSP. AND EXP.	TOTAL	MEAN	INSP. AND EXP.	TOTAL	MEAN	INSP. AND EXP.	TOTAL	MEAN
20	-3.8 -7.8	4	-5.8	-7.8 -12.8	5	-10.3	+2.4 -8.8	11.2	-3.2
21	-3.6 -13.0	9.4	-8.3	-1.2 -15.0	13.8	-8.1	+5 -15	20	-5
22	-1 -5	4	-3	+ .4 -6.2	6.6	-2.9	+6.4 -14	20.4	-3.8
25	-1 -5.4	4.4	-3.2	-1 -5.8	4.8	-3.4	+2.6 -7.0	9.6	-2.2
26	-12* -14.6	2.6	-13.3	-11 -16.4	5.4	-13.7	+1.6 -3	4.6	- .7
27	-1 -8	7	-4.5	+8.4 -20.6	29	-6.1	+5 -17	22	-6
28	-3.4 -13.2	9.8	-8.3	- .6 -12.4	11.8	-6.5	+3.8 -5.8	9.6	-1
30	-2.2 -8	5.8	-5.1				+3.6 -8.2	11.8	-2.3
31	-2.4 -10	7.6	-6.2				+2.4 -7	9.4	-2.3
32	-2.6 -9.2	6.6	-5.9				+3.1 -8.2	11.3	-2.6
33	-2.6 -6.4	3.8	-4.5				+9.6 -12.4	22	-1.4
34	-2.8 -7.8	5	-5.3				+1.6 -6.2	7.8	-2.3
36	-4.6 -7.2	2.6	-5.9				+3.6 -5.8	9.4	-1.1
15	-1.0 -4.0	3	-2.5				+8.0 -1.0	9	+3.5
35	-2.2 -8.4	6.2	5.3				+ .4 -4.2	4.6	-1.9

Animals Vagotomized Before Congestion

29	-2.1 -14.2	12.1	-8.05				+10.6 -22.4	33	-5.9
38	0	10.4	-5.2	+5.8 -17	22.8	-5.6	+9 -16.8	25.8	-3.9
39	-2.4 -11.2	8.8	-6.8				+2.4 -16	18.4	-6.8
A. B. V. 45	+ .5 -15.6	16.1	-7.55				+3.6 -17	20.6	-6.7
A. V. C.							+1.8 -12	13.8	-5.1

A. B. V. = After bilateral vagotomy.

A. V. C. = After vagotomy and cocainization of carotid bodies.

*The markedly negative pressures in this animal occurred after instillation of iodized oil into the bronchi for visualization of the bronchial tree by x-ray.

the mean intrapleural pressure rose toward or above atmospheric levels. This was a constant phenomenon and confirms the work of Christie and Meakins,¹ who found similar results in patients with pulmonary congestion due to heart disease.

Alterations in Tidal Exchange and Ventilation.—The tidal exchange rose progressively during the administration of carbon dioxide, in some cases increasing by over 100 per cent (Table III). Similarly, ventilation was markedly augmented after the inhalation of carbon dioxide, occasionally increasing over threefold (Table IV). During increasing pulmonary congestion the tidal air, after a brief rise in many animals, decreased progressively (Table III and Fig. 1). The respiratory rate rose sharply in all animals during the early stages of congestion; during the terminal stages breathing became slow and labored. Corresponding to the changes in respiratory rate and the initial increase in tidal exchange, ventilation per minute rose during the early phases of infusion; later declining gradually, sometimes to values near or below the original resting levels (Table IV).

TABLE III. AVERAGE TIDAL EXCHANGE IN C.C. PER SQUARE METER

DOG NO.	RESTING	AFTER CO ₂ INHALATION	DURING MAXIMUM PULMONARY CONGESTION
15	95	—	60
20	282	510	194
21	331	646	174
22	208	360	92
25	95	182	56
26	194	249	75
27	242	520	155
28	300	580	135
30	122	—	61
31	84	—	55
32	203	—	98
33	118	—	103
34	122	—	113
35	340	—	175
36	184	—	108

Animals Vagotomized Before Congestion and CO₂

29	445	—	191
38	330	615	287
39	330	—	308
A. B. V.	141	—	367
45	—	—	—
A. V. C.	—	—	253

A. B. V. = After bilateral vagotomy.

A. V. C. = After vagotomy and cocainization of carotid bodies.

Changes in Respiratory Efficiency.—To determine the efficiency of respiration, the amount of tidal exchange (in cubic centimeters) produced per centimeter of change in intrapleural pressure was used as an index of efficiency:

$$\left(\frac{\text{Tidal exchange in cm.}^3 \text{ per square meter}}{\text{Total intrapleural pressure change per breath in cm. H}_2\text{O}} \right)^*$$

By this method of determining respiratory efficiency it was found that during the administration of carbon dioxide the amount of tidal air breathed, for each centimeter of intrapleural pressure change, increased progressively from the resting state (Table V and Fig. 2).

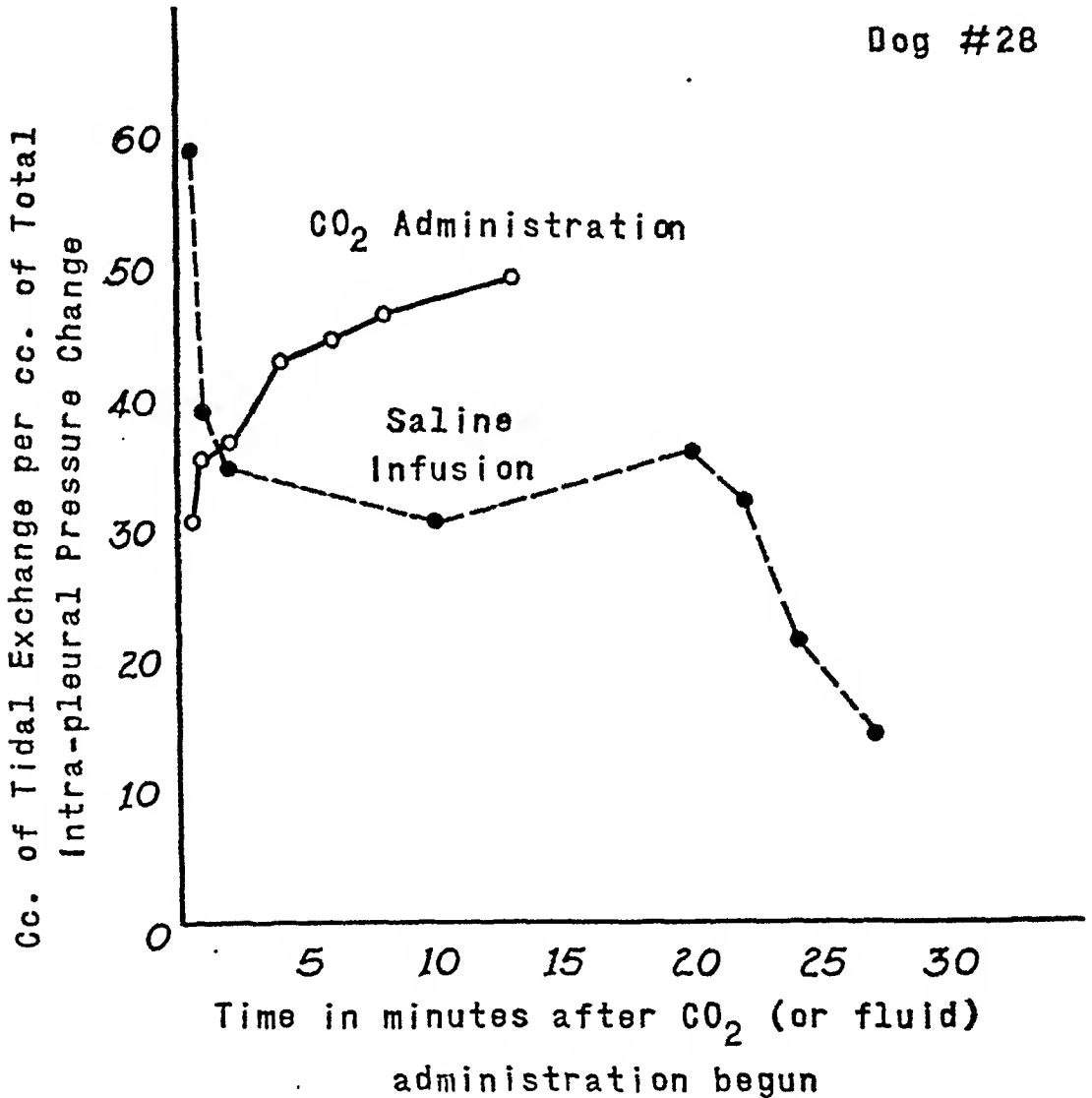


Fig. 2.—Graph showing alterations in tidal exchange produced for each centimeter of total change in intrapleural pressure. The tidal exchange per centimeter of intrapleural pressure change rises rapidly after carbon dioxide inhalation and falls progressively during intravenous infusion.

*This method of measurement of distensibility, or efficiency, involves the assumption that recoil from compression of the lungs during expiration is negligible. An alternate method of measuring intrapleural pressure changes is that of using only the negative pressure developed as an index of the force applied to the lungs. Since, in many cases, the portion of the pressure curve which was positive was very large, this latter assumption was obviously not feasible. It has been shown¹ that, although there is a slight amount of recoil after compression of the lungs, it is small in amount and we therefore have chosen to disregard it.

During pulmonary congestion caused by venous infusion, however, it will be seen (Table V, Fig. 2) that the amount of tidal exchange per centimeter of intrapleural pressure change decreased markedly at the height of pulmonary congestion. The response after carbon dioxide is evidence of increasing efficiency of respiration in the normal lung when an increasing stimulus is applied. On

EFFICIENCY OF RESPIRATION, EFFECT OF 5% CO₂ INHALATION AND EXPERIMENTAL PULMONARY CONGESTION IN VAGOTOMIZED ANIMAL

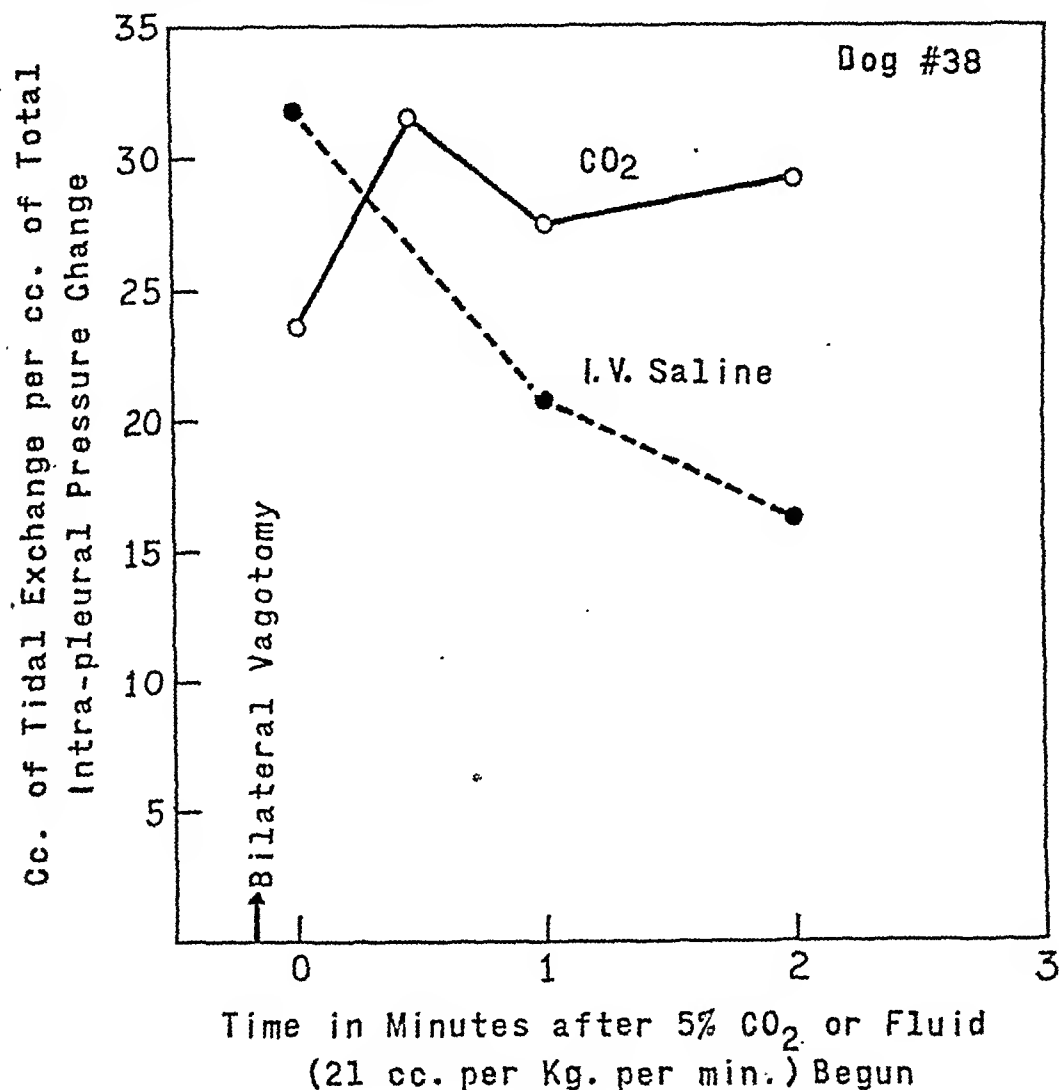


Fig. 3.—Vagotomized animal. Graph showing alterations in tidal exchange produced for each centimeter of total change in intrapleural pressure. The tidal exchange rises after carbon dioxide, and falls progressively during intravenous infusion. These findings are similar to those in the nonvagotomized animal (Fig. 2).

the other hand, although gross hyperpnea had supervened during pulmonary congestion, and although the intrapleural work expended had increased progressively, the efficiency of respiration and the amount of tidal exchange diminished rapidly during congestion.

TABLE IV. VENTILATION IN LITERS PER SQUARE METER PER MINUTE

DOG NO.	RESTING	AFTER CO ₂ INHALATION	DURING MARKED PULMONARY CONGESTION
15	4.86	—	1.80
20	4.5	12.1	1.26
21	2.32	9.1	2.42
22	2.48	8.50	1.84
25	2.33	6.75	1.80
26	2.72	5.95	2.12
27	5.8	15.1	3.4
28	3.60	10.50	4.85
30	1.47	—	1.22
31	1.76	—	.88
32	3.05	—	1.66
33	1.41	—	1.54
34	3.50	—	2.70
36	1.47	—	2.76
35	4.09	—	3.50

Following Bilateral Vagotomy

29	3.11	—	0.38
38	2.64	6.76	1.75
39	2.64	—	3.77
A. B. V.	1.65	—	1.10
45	—	—	—
A. V. C.	—	—	1.01

A. B. V. = After bilateral vagotomy.

A. V. C. = After vagotomy and coagulation of carotid bodies.

TABLE V. RESPIRATORY EFFICIENCY $\frac{\text{CM.}^3 \text{ OF TIDAL EXCHANGE PER SQUARE METER}}{\text{TOTAL INTRAPLEURAL PRESSURE CHANGE (CM. H}_2\text{O)}}$

DOG NO.	RESTING	AFTER CO ₂ INHALATION	DURING MAXIMUM PULMONARY CONGESTION
15	31.6	—	6.6
20	47.5	10.5	17.3
21	35.1	46.8	8.7
22	52.1	54.6	4.6
25	21.6	38.3	5.8
26	51.1	65.5	17.8
27	24.2	34.7	7.0
28	30.6	49.2	14.0
30	21.1	—	5.18
31	11.0	—	5.9
32	31.5	—	8.70
33	31.0	—	8.8
34	25.5	—	14.3
35	54.9	—	36.4
36	31.6	—	11.5

Respiratory Efficiency Following Bilateral Vagotomy

29	36.8	—	5.79
38	31.7	—	11.10
39	38.4	28.5	36.6
A. B. V.	25.7	—	17.8
45	—	—	—
A. V. C.	—	—	18.35

A. B. V. = After bilateral vagotomy.

A. V. C. = After vagotomy and coagulation of carotid bodies.

Chemical Alterations in the Blood.—Since the administration of large quantities of 0.9 per cent sodium chloride solution in a short period of time lowers the pH of the blood,⁴⁻⁷ determinations of pH, arterial oxygen saturation, and serum carbon dioxide tension were made in these animals. In addition to 0.9 per cent sodium chloride solution, some animals were perfused with fluids containing a known amount of fixed base (solutions of 28 and 60 millimols of sodium bicarbonate per liter, rendered isotonic with sodium chloride) in an attempt to prevent the fall in pH of the blood, and the effects upon respiration were observed. Regardless of the chemical alterations in the blood (Table VI), the changes in mechanical efficiency of respiration were exactly parallel in the different animals, the efficiency of respiration diminishing progressively. Similarly, despite the different types of infusion, the tidal air decreased and the intrapleural pressure rose in all animals.

FOLLOWING BILATERAL VAGOTOMY

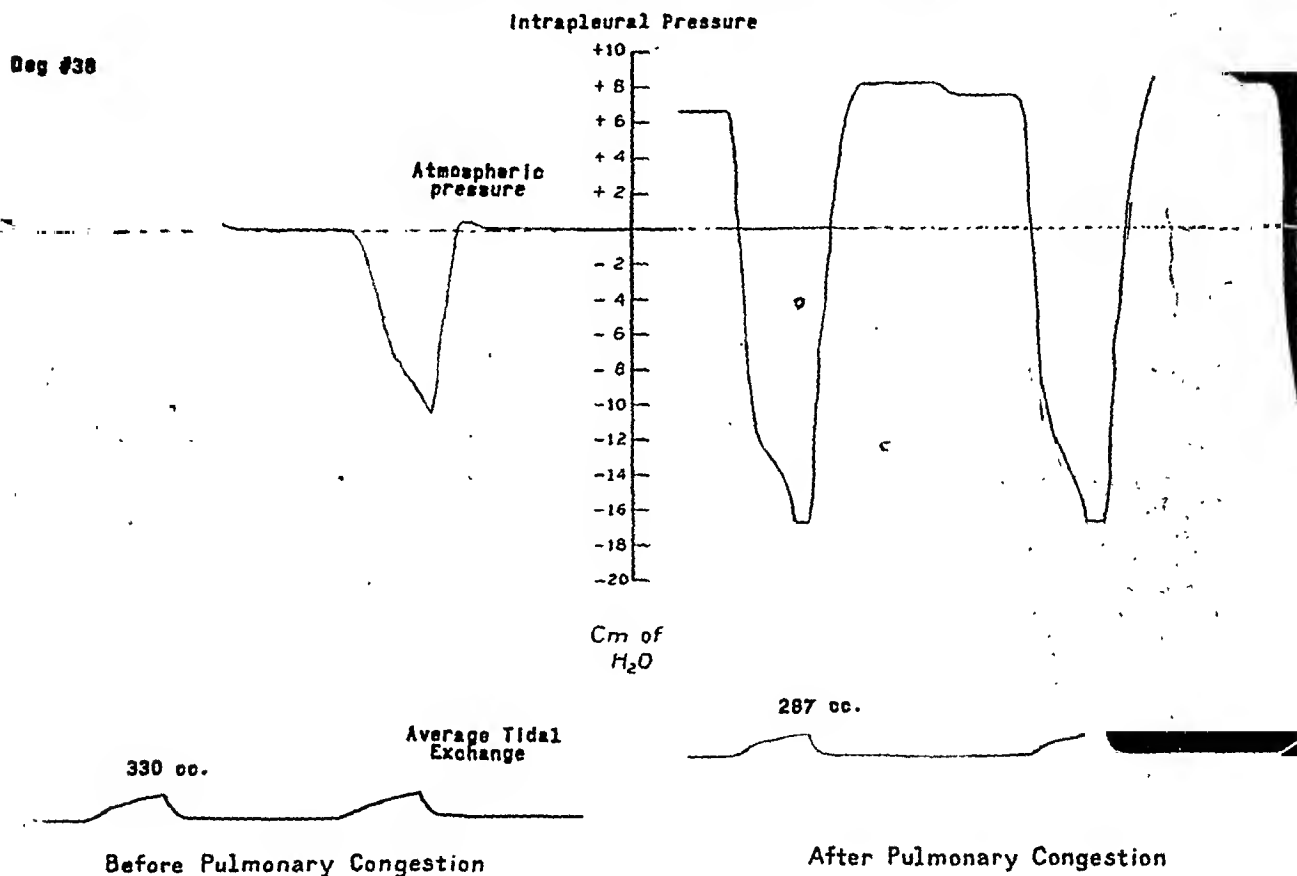


Fig. 4.—After vagotomy in the resting animal the respiratory rate slows, but expiratory pressure remains at atmospheric levels. After infusion of the vagotomized animal the total intrapleural pressure excursions increase markedly and the expiratory pressure rises well above atmospheric, while the tidal exchange (expressed per square meter of surface area) diminishes. The respiratory rate does not increase during infusion.

Effect of Vagotomy and Cocainization of Carotid Body and Sinus.—Vagotomy was performed on five animals which were then subjected to rapid venous infusions, producing pulmonary congestion. Vagotomy did not prevent either the

TABLE VI. CHEMICAL ALTERATIONS IN THE BLOOD

ANIMAL	INFUSING FLUID	BEFORE INFUSION			AFTER INFUSION			RESULTS
		pH	SERUM CO ₂ TENSION (MM.-HG)	ARTERIAL SATURATION (PER CENT)	pH	SERUM CO ₂ TENSION (MM.-HG)	ARTERIAL SATURATION (PER CENT)	
28 (Bilateral vagotomy)	0.9% solution of Sodium Chloride	7.56	22.7	90.1	7.05	48.5	90.5	Progressive decrease in respiratory efficiency and tidal air, rise in intrapleural pressure
29	0.9% solution of Sodium Chloride	7.65	20.2	88.5	7.46	17.06	90.1	
30	5 Gm. NaHCO ₃ 5.55 Gm. NaCl/liter	7.3	51.4	92.1	7.3	69.7	91.8	
34	5 Gm. NaHCO ₃ 5.55 Gm. NaCl/liter	7.3	36.6	90.1	7.3	85.4	90.8	
35	1.25 Gm. NaHCO ₃ 7.30 Gm. NaCl	7.5	28.0	91.2	7.42	31	91.1	
45 Vagotomy and cocainization of carotid bodies	0.9% Sodium Chloride	7.30			6.80			

marked increase in intrapleural pressure fluctuations, with the shift of expiratory pressure readings above the atmospheric level, or the elevation of mean intrapleural pressures toward atmospheric levels (Table II, Fig. 4). The acceleration of the respiratory rate, which was seen in the intact animal, however, was not observed. Nevertheless, the efficiency of respiration (measured by the tidal exchange per centimeter of water of intrapleural pressure change) diminished progressively during infusion, after bilateral vagal section (Fig. 3).

Since the pH of the blood was found to fall markedly during the administration of 0.9 per cent sodium chloride, it seemed desirable to determine the extent to which peripheral chemoceptor mechanisms were stimulating respiration. Dog 45 was vagotomized and perfused rapidly with saline; Table II reveals that the total intrapleural pressure fluctuations increased markedly after infusion, while the expiratory and mean intrapleural pressures also rose. During the infusion, the pH of the blood fell markedly; from 7.30 to 6.80 (Table VI). Immediately after cocainization of the nerves to the carotid body and sinus, total intrapleural pressure fluctuations decreased markedly. Since the interruption of sensory impulses from the carotid sinus has been shown to stimulate respiration⁸ this decrease in the motor activity of the respiratory muscles was considered as being caused by the blocking of impulses arising from stimulation of the carotid bodies, produced by the increase in hydrogen ion concentration. Thus, at least with the administration of large quantities of 0.9 per cent sodium chloride solution, peripheral chemoceptor mechanisms played a very important role in stimulating the respiratory center.

Effect of Section of the Cervical Cord.—Section of the spinal cord in the lower cervical region was performed at the height of congestion to abolish active expiratory movements. In each case an immediate sharp drop in tidal exchange occurred, sometimes to negligible levels (Table VII). Total intrapleural pressure

TABLE VII. EFFECT OF SECTION OF CERVICAL SPINAL CORD UPON RESPIRATION DURING PULMONARY CONGESTION

DOG NO.	TIDAL EXCHANGE (C.C.PER SQUARE METER)		INTRAPLEURAL PRESSURE CM. H ₂ O		TOTAL INTRAPLEURAL PRESSURE (FLUCTUATION CM. H ₂ O)	
	BEFORE CORD SECTION	AFTER CORD SECTION	BEFORE CORD SECTION	AFTER CORD SECTION	BEFORE CORD SECTION	AFTER CORD SECTION
30	61	27	+3.6 Exp. -8.2 Insp.	-1.4 Exp. -8.6 Insp.	11.8	7.2
31	55	No measurable ex- change within 30 sec.	+2.4 Exp. -7.0 Insp.	+0.4 Exp. -1.8 Insp.	9.4	2.2
32	98	49.8	+3.1 Exp. -8.2 Insp.	-1.4 Exp. -6.1 Insp.	11.3	4.7
36	108	10	+3.6 Exp. -5.8 Insp.	+2.4 Exp. -4.2 Insp.	9.4	6.6

TABLE VI. CHEMICAL ALTERATIONS IN THE BLOOD

ANIMAL	INFUSING FLUID	BEFORE INFUSION			AFTER INFUSION			RESULTS
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34	5 Gm. NaHCO ₃ 5.55 Gm. NaCl/liter	7.3	36.6	90.1	7.3	85.4	90.8	
35	1.25 Gm. NaHCO ₃ 7.30 Gm. NaCl	7.5	28.0	91.2	7.42	31	91.1	
45 Vagotomy and cocainization of carotid bodies	0.9% Sodium Chloride	7.30	—	—	6.80	—	—	

marked increase in intrapleural pressure fluctuations, with the shift of expiratory pressure readings above the atmospheric level, or the elevation of mean intrapleural pressures toward atmospheric levels (Table II, Fig. 4). The acceleration of the respiratory rate, which was seen in the intact animal, however, was not observed. Nevertheless, the efficiency of respiration (measured by the tidal exchange per centimeter of water of intrapleural pressure change) diminished progressively during infusion, after bilateral vagal section (Fig. 3).

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TABLE VII. EFFECT OF SECTION OF CERVICAL SPINAL CORD UPON RESPIRATION DURING PULMONARY CONGESTION

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	BEFORE CORD SECTION	AFTER CORD SECTION	BEFORE CORD SECTION	AFTER CORD SECTION	BEFORE CORD SECTION	AFTER CORD SECTION
30	61	27	+3.6 Exp. -8.2 Insp.	-1.4 Exp. -8.6 Insp.	11.8	7.2
31	55	No measurable ex- change within 30 sec.	+2.4 Exp. -7.0 Insp.	+0.4 Exp. -1.8 Insp.	9.4	2.2
32	98	49.8	+3.1 Exp. -8.2 Insp.	-1.4 Exp. -6.1 Insp.	11.3	4.7
36	108	10	+3.6 Exp. -5.8 Insp.	+2.4 Exp. -4.2 Insp.	9.4	6.6

fluctuations diminished considerably; in some cases the expiratory intrapleural pressures diminished, but did not fall below atmospheric levels in all animals. If rapid venous infusion was continued in the animals in which abolition of expiratory movements caused a fall in expiratory intrapleural pressure levels, the mean and expiratory pressures again rose toward or above the atmospheric level (Fig. 5).

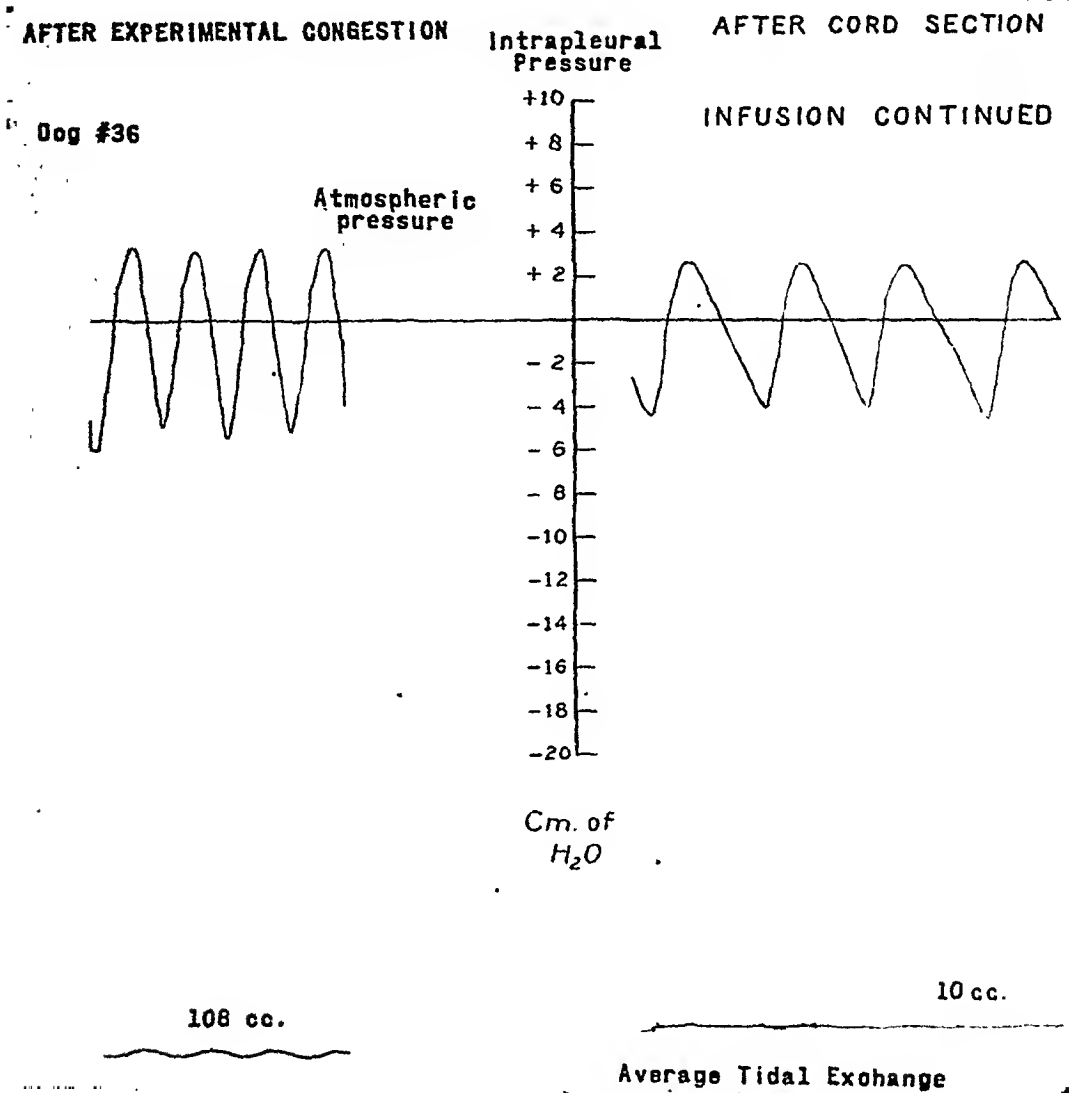


Fig. 5.—After section of the cervical cord (abolishing active expiratory movements) the expiratory intrapleural pressure remains above the atmospheric level if the intravenous infusion is continued, and the tidal exchange and ventilation fall to very low levels.

DISCUSSION

The importance of local changes in lung tissues in causing the labored and difficult respiration of pulmonary congestion seen in heart disease was pointed out in 1886 by von Basch,¹⁰ who stated that while alveolar space and lung size increased after congestion of the lung, rigidity (Lungenstarrheit) of the pulmonary tissues also increased. Traube¹¹ contended, on the contrary, that en-

largement of the pulmonary vessels and their protrusion into alveolar spaces, with decrease in size of the latter, was the cause of the labored respiration. In 1927 Binger¹² proved that the lungs of patients with congestive failure contained an increased amount of residual air, which diminished in very severe congestion. In 1929 Churchill and Cope,¹³ by producing experimental congestion of the lungs in animals, proved the role of nervous influences in causing a rapid and shallow type of respiration. Harrison¹⁴ and co-workers further proved that the most important stimulus to rapid and shallow breathing seen in pulmonary congestion arose from vagal reflexes, not only in the pulmonary tissues but also from increased pressure in the great venous trunks of the heart and in the right auricle. Christie and Meakins,¹ in 1934, endeavored to correlate these observed phenomena by suggesting that the increased rigidity of the pulmonary tissues was caused by increased tension, and that the latter stimulated vagal endings, rendering the Hering-Breuer reflex hyperactive.

The present study indicates that as pulmonary congestion increases, the respiratory mechanism operates with progressively decreasing efficiency, expending a greater amount of work for a diminishing amount of tidal air per breath, and that these changes are independent of vagal reflexes. Christie and Meakins,¹ while demonstrating that elastic recoil of the lung was only moderately changed in pulmonary congestion due to heart disease, showed in patients that a greater fluctuation in intrapleural pressure was needed to achieve a given amount of tidal exchange, and stated that this was due to diminished "distensibility" of the lung.

It was further shown in the present study that, although the increase in respiratory rate after rapid infusion was prevented by bilateral vagotomy, the marked increase in intrapleural pressure changes and the diminished efficiency demonstrated after infusion were not prevented by section of the vagi. Since the extent of intrapleural pressure fluctuations was markedly diminished by cocaineization of the nerves of the carotid body and sinus, it seems probable that a great portion of the reflex stimulation of respiration in the animals given 0.9 per cent sodium chloride was due to stimulation of peripheral chemoceptor organs by the fall of pH of the blood, caused by dilution of body base. Although the stimuli to breathing produced by rapid intravenous infusion were not further delineated in these studies, it is possible that they were multiple in nature. Among these possible sources should be considered (1) the effect of a lowered pH on the respiratory center itself,¹⁵ (2) the effect of increased venous pressure in the cranial cavity,¹⁶ and (3) stimulation of afferent fibers carried by the spinal cord from blood vessels in the limbs. In connection with the latter possibility, Moyer⁹ has recently shown that distention of peripheral veins accelerates breathing in the nonvagotomized animal. The marked venous distention observed in the animals in the present study may have been a contributing factor in increasing the respiratory rate. Regardless of the origin of the afferent impulses stimulating respiration, the motor functions of respiration operated with decreased efficiency whenever pulmonary congestion was produced.

What are the factors responsible for this increased resistance to pulmonary filling and emptying? Von Neergaard and Wirz¹⁷ have shown that the physical factors within the lungs which may alter their filling may reside in (a) the upper airway; (b) the lower airway and alveoli; and (c) the resistance of the pulmonary tissues themselves to deformation ("Deformationswiderstand"). Since in these experiments there was no alteration in the upper airway, it becomes evident that the causes of increased respiratory efficiency after carbon dioxide administration, and the decreased efficiency after experimental congestion, should be sought in changes in the smaller air passages and alveoli, and/or in the resistance of the pulmonary tissues to changes in shape and size. Since the physical properties of normal pulmonary tissues were apparently unaltered by carbon dioxide, it seems likely that enlargement of smaller bronchi and bronchioles occurred, resulting in a decreased frictional resistance to the entrance of air, and thus increasing respiratory efficiency. After congestion of the lungs, however, the efficiency of respiration fell progressively. Hence, alterations in either the size of smaller air passages and alveoli, and/or in the resistance of the tissues (to change of shape and size) must be assumed to have occurred with pulmonary congestion.

If the lungs and their vessels are considered as analagous to a type of erectile tissue, the resistance of the pulmonary tissues to changes in size and shape is readily understood. Von Basch's original demonstration that filling of the vessels of the excised lung caused an increase in lung size, with an actual increase in the air-containing space of the lung, indicated that as the vessels became distended and turgid they acted as an expanding, semirigid framework which increased the size of the enclosed air spaces. This finding was confirmed by Romanoff,¹⁸ who also found that air entered the excised lung when the pulmonary vessels were filled with fluid. Weiss and Robb,¹⁹ after extensive studies on patients with severe pulmonary congestion and cardiac asthma, concluded that the chest assumed a position of "functional emphysema" with the diaphragm fixed in an inspiratory position, and that an actual increase in total residual air occurred. Likewise, Binger¹² demonstrated an increase in residual air in patients with pulmonary congestion due to heart disease. The findings of the latter three authors can only be explained by the development of an increase in lung volume and air space caused by the erectile nature of the tissues of the congested lung.

When the changes in ventilation are considered in the light of the preceding findings, the cause of the increased effort exerted to achieve an adequate tidal exchange is easily understood. With increasing pressure in the lung vessels caused by the rapid infusions, the properties of resistance of the tissues to changes in shape and size became much enhanced. A much greater change in pressure had to be exerted upon the surface of the congested lung to produce expansion during inspiration. Similarly, during expiration the lung had to be actively compressed by an active contraction of the expiratory muscles to supplement the elastic recoil of the lung and to permit air to be expelled. As the turgidity of the pulmonary vessels increased, with mounting pulmonary congestion, the ventilation accomplished in relation to the work expended (measured by the

intrapleural pressure changes in inspiration and expiration) became progressively less. This concept is in exact accord with the observation of a marked decrease in the efficiency of respiration seen in these experiments with increasing pulmonary congestion.

The development of an enlarged semirigid lung imposes certain further mechanical disadvantages upon ventilation. A corollary to the demonstration of Weiss and Robb¹⁹ that the congested lung becomes fixed in an inspiratory position is the development of a marked diminution of both complemental and supplemental air. Optimal tidal exchange then became possible only if total lung size were decreased by active compression of the lung by the expiratory muscles; reserve air had to be expelled by active effort from the air spaces before a maximal amount of air could enter the lung in the following inspiration. Proof of the vital role of the expiratory muscles in this regard was seen in the present study in the sharp diminution of tidal exchange which occurred immediately after the abolition of expiratory movements by section of the cervical cord.

The increased activity of expiratory muscles has certain other important connotations. In previous work one of us²⁰ has shown that pulmonary congestion caused by heart disease produced a labored type of respiration, with especial difficulty in expiration, and that the expiratory difficulty is much diminished by the administration of a bronchodilating drug (aminophylline). Although no direct observations of this type were made in the present study, our previous observations in patients suggest that a portion of the extra work expended to achieve ventilation in these animals, especially during expiration, was due to relative diminution in size of the smaller air passages. A further effect of the forced pulmonary compression by expiratory muscles is the facilitation of emptying of the congested pulmonary bed. Barach and Swenson²¹ have shown clearly that an increase in intrapulmonary pressure during the expiratory phase exerts such an emptying effect upon the pulmonary circulation, and have made use of this principle in the treatment of pulmonary congestion and pulmonary edema.

Viewed in the light of the increased muscular activity demonstrated in the present studies in both inspiration and expiration during pulmonary congestion, the sensation of dyspnea in patients is more readily understood. In both phases of breathing the respiratory muscles are called upon to exert an unusual degree of effort, and also to operate at a definite mechanical disadvantage. Moreover, this increased activity must proceed over a relatively long period of time to insure the preservation of adequate ventilation. When the effort necessary to accomplish ventilation in the congested lung becomes very great, and when such exertion is prolonged, fatigue of the respiratory muscles occurs and the conscious recognition of this sensation of distress must inevitably follow. Moyer⁹ has described the feeling of dyspnea as "a sense of specialized fatigue," an apt description of the series of events that occurs. Vagal reflexes control the rate and depth of respiration, terminating inspiration abruptly in the congested lung. This vagal control, however, would not seem to affect the relative disproportion between the work expended and the diminished tidal exchange achieved in pulmonary congestion. In this excessive effort necessary to ventilate the

congested lung, and in the fatigue resulting therefrom, would seem to lie the genesis of the complex sensation of dyspnea.

The shift in mean intrathoracic pressure toward atmospheric levels and above is not wholly due to increased activity of expiratory muscle groups, since abolition of their action did not cause the excursions above the atmospheric level to cease. Hence, although a portion of the upward shift may be due to these muscles, an increase in intrathoracic tension caused by overdilatation of pulmonary vessels must also be an important factor. Traube's¹¹ contention that the congested capillaries encroach upon the alveoli, thus decreasing air space, is supported by the finding of a rapid fall in tidal exchange accompanied by a progressive rise in intrapleural pressure, in the terminal stages of pulmonary congestion in these animals. During extreme pulmonary congestion, even though intrapleural pressure fluctuations increased markedly, tidal exchange diminished precipitously, suggesting that alveolar air space was decreased in size by projection of the engorged pulmonary vessels into the alveolar lumen, or that the alveolar space itself remained unchanged but became filled with edema fluid. Binger¹² has also shown in patients that in advanced pulmonary congestion the residual air, which was at first increased, undergoes a diminution in volume. It seems probable, therefore, that diminution in alveolar space occurs but appears only in the later stages of severe pulmonary congestion.

CONCLUSIONS

1. A reconstruction of the dynamic changes in respiration from these studies indicates that the following events occur in pulmonary congestion:

(a) Accompanying the congestion, the pulmonary tissues undergo a marked increase in resistance to changes in shape and size. It is probable that relative obstruction also develops in the smaller air passages.

(b) Concomitant with the events in (a), increasing tension in the pulmonary tissues causes stimulation of vagal nerve endings, producing an acceleration of respiration and rendering the Hering-Breuer reflexes more sensitive.

(c) Tidal exchange is then accomplished in the congested and turgid lung at the expense of total greater changes in intrapleural pressure.

(d) As distention of pulmonary vessels and tissues with fluid increases, mean intrathoracic pressure rises toward atmospheric levels and expiratory intrapleural pressures rise well above the atmospheric level.

(e) Active participation of the expiratory muscle groups occurs when pulmonary congestion becomes marked. This increased activity is necessary to achieve optimal tidal exchange in the congested lung.

(f) These changes appear to be independent of alterations in carbon dioxide and hydrogen ion concentration of the blood.

2. In the intact animal the increase in respiratory rate with massive venous infusions is mainly of vagal origin, although the effect of increased pressure in the veins of the body and cranial cavity may play a contributory role in accelerating breathing.

3. Since rapid infusion of vagotomized animals produced marked increased in intrapleural pressure fluctuations, it is evident that the respiratory stimulation produced by such infusions arises not only from impulses mediated via the vagi, but also through other means.

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PROLONGATION OF THE Q-T INTERVAL IN THE ELECTRO-CARDIOGRAM OCCURRING AS A TEMPORARY FUNCTIONAL DISTURBANCE IN HEALTHY PERSONS

WITH A PROPOSAL THAT (Q-T) CAL. MAY BE USED TO DESIGNATE Q-T INTERVALS CALCULATED FOR THE PHYSIOLOGIC VARIABLES, CYCLE LENGTH, AGE, AND SEX

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VARIATIONS in the Q-T interval in the electrocardiogram may be due to several factors in addition to the heart rate. It is generally agreed that shortening of Q-T may result following the administration of digitalis¹ and that lengthening may be associated with hypocalcemia,² quinidine poisoning,² low blood potassium,³ familial periodic paralysis,³ beriberi,⁴ diabetic coma,⁵ cardiac enlargement,⁵ and heart failure of various types.

In view of the increasing clinical significance now being ascribed to variations in the Q-T interval, it seems worthwhile to record the observation that Q-T may become temporarily prolonged in healthy persons as a result of the functional alterations associated with change in body position. This phenomenon was first observed in the course of examining an aviation cadet referred to us because of the complaint of postural dizziness.

The Q-T interval of the electrocardiogram became greatly prolonged, relative to the heart rate, when the aviator was tilted from the horizontal to a head-up position. Because of this Q-T finding, a further study was made.

Q-T TERMINOLOGY

Inasmuch as the duration of Q-T is affected by important physiologic variables, these relationships have been expressed by a number of empirical formulas. In these formulas, Q-T is allowed to vary with the square root,⁶ cube root,³ or logarithm⁷ of the cycle length, and age and sex are taken into account by introducing a correction either in the formula itself or in the value derived from the solution of the formula. In this manner, Q-T is, in effect, calculated from certain physiologic variables and is sufficiently constant to provide a reference for the study of other variables which may affect Q-T duration.

This work was carried out at the School of Aviation Medicine and Research, Naval Air Station, Pensacola, Florida.

The opinions or assertions contained herein are the private ones of the writers, and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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This calculated Q-T is variously designated. It is sometimes referred to as the systolic index, which expresses its relationship to the duration of systole; frequently it is referred to simply as Q-T, and the reader must determine whether the actual or calculated value is implied. We suggest, therefore, that the subscript "cal." (an abbreviation of calculated) be used to designate the Q-T interval which has been calculated from the physiologic variables according to one of the several proposed formulas. Thus, the general meaning of Q-T cal. would always be understood, and it would acquire more specific meaning if reference were made to the particular formula used in obtaining Q-T cal. values.

Q-T cal. is distinguished from the corrected Q-T (Q-T_c) of Taran and Szilagyi⁸ as follows:

$$\begin{aligned} \text{Taran and Szilagyi's Q-T}_c &= \frac{\text{actual Q-T}}{\sqrt{\text{cycle length}}} \\ \text{Q-T cal.} &= K \sqrt{\text{cycle length}} \end{aligned}$$

METHOD

Ten aviation cadets between the ages of 19 and 28 years served as subjects. All were healthy and without complaint except one (Case 1), who complained of loss of vision on suddenly standing erect, and of ease of blackout during certain flight maneuvers.

Each subject was allowed to lie on the tilt table for at least fifteen minutes, and a control electrocardiogram was taken at the end of this period. Lead II was then recorded (1) while the subject was tilted 60° head up, (2) during the first and fifth minutes after the tilt, and (3) while the subject was tilted back to the horizontal position. Careful measurements were made of the duration of Q-T and of cycle length, and the relationship between them was calculated using Bazett's formula,⁶ $Q-T = 0.392 \sqrt{\text{cycle length}}$, and Ashman's formula for adult men,⁷ $Q-T = 0.375 \times \log 10 (\text{cycle length} + 0.07)$.

RESULTS

A review of the several records obtained in each case showed that the maximum changes in Q-T cal. as compared with those in the actual Q-T occurred immediately after the subject was tilted. A summary of these maximal changes calculated both according to the formula of Bazett and that of Ashman is shown in Table I. It is seen that the changes are marked in one case, moderate in four, slight in four, and insignificant in one case. The electrocardiograms illustrating the greatest change (Case 1) are shown in Fig. 1. In the record taken immediately after the subject was tilted (Fig. 1,B) it is seen that the cycle length is greatly shortened, but that the duration of Q-T remains nearly the same. Thus, the change in the relationship of Q-T and cycle length is due to the failure of Q-T to shorten to a degree commensurate with the increase in heart rate. A

return toward the normal is seen in Fig. 1,C, taken nine minutes after the subject had been tilted. The same was true in varying degree for all other cases save one.

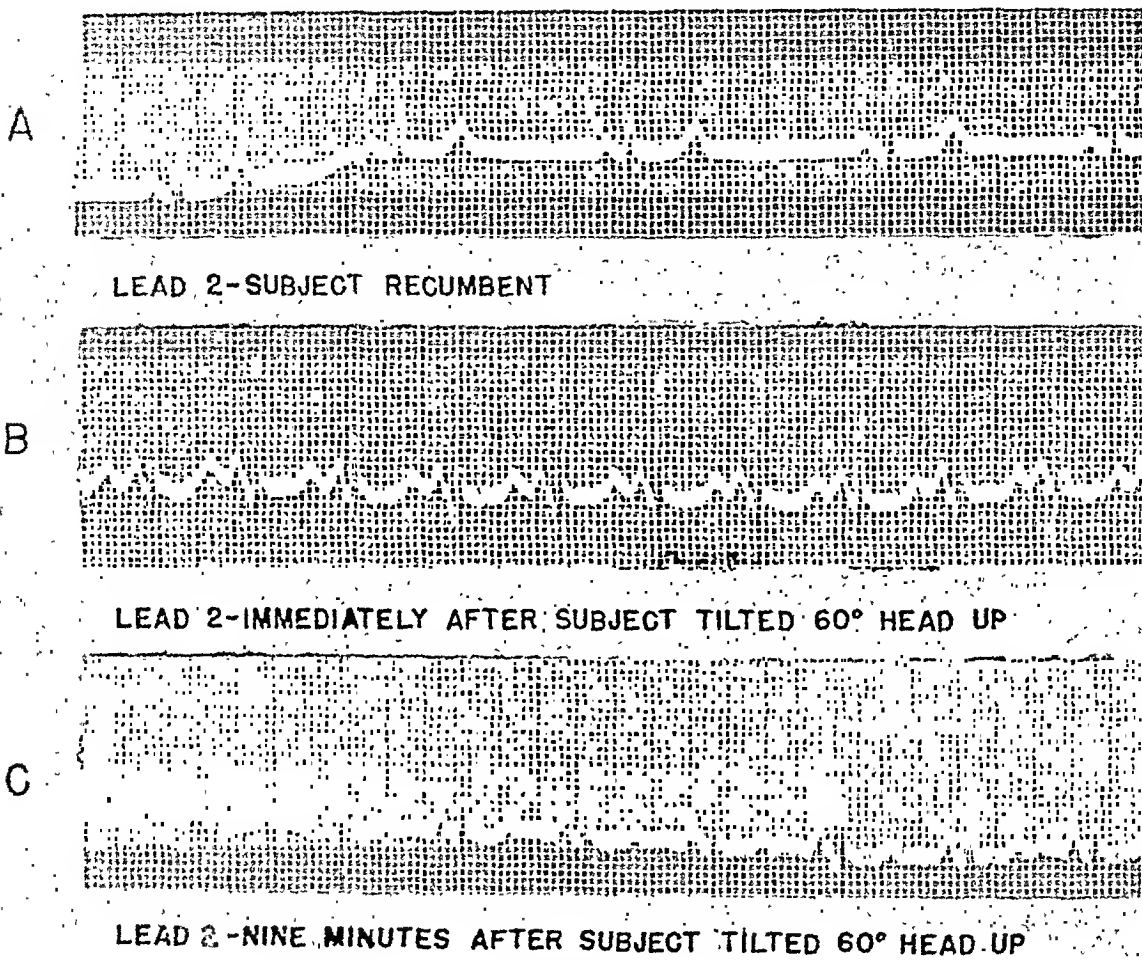


Fig. 1.—Case 1. Effects of postural change on electrocardiogram.

TABLE I. EFFECTS OF CHANGE OF POSTURE ON THE Q-T INTERVALS OF TEN HEALTHY YOUNG MEN

CASE NO.	CYCLE LENGTH		ACTUAL Q-T		Q-T cal.		Q-T cal		DECREASE ON TILT OF		ACTUAL Q-T
	FLAT	TILT	FLAT	TILT	FLAT BAZETT	TILT	FLAT ASHMAN	TILT	BAZETT'S Q-T cal.	ASHMAN'S Q-T cal	
1	1.36	.57	.48	.46	.46	.30	.44	.31	.16	.13	.02
2	.98	.73	.40	.40	.39	.34	.39	.35	.05	.04	.00
3	.68	.60	.32	.32	.32	.30	.34	.32	.02	.02	.00
4	.95	.65	.35	.33	.38	.32	.39	.33	.06	.06	.02
5	.60	.51	.32	.29	.30	.28	.32	.29	.02	.03	.03
6	.87	.77	.37	.36	.37	.34	.38	.36	.03	.02	.01
7	.84	.84	.35	.36	.36	.36	.37	.37	.00	.00	.01
8	.84	.68	.34	.32	.36	.32	.37	.34	.04	.03	.02
9	1.00	.81	.34	.34	.39	.35	.40	.36	.04	.04	.00
10	1.06	.62	.38	.30	.40	.31	.41	.32	.09	.09	.08

COMMENT

Since the Q-T interval represents the period of electrical ventricular systole (that is, from the time of the beginning of depolarization of the upper interventricular septum until the time of repolarization or the restitution of the polarized state in the ventricular septum and apical regions of the heart) we apparently are dealing, in these cases, with a retardation of the repolarizing process, such as might be produced by a decrease in the number of calcium ions in the blood. An explanation for the occurrence of this phenomenon in our cases is extremely difficult. It is reasonable to think that it might be due to sympathetic or parasympathetic influence, inasmuch as the relative change in Q-T occurs within a few seconds. Nevertheless, such a conclusion can only be verified by future electrocardiographic studies. Observations of the Q-T following the administration of such drugs as mecholyl, atropine, and epinephrine might provide a clue.

The influence of posture on the electrocardiogram has been studied previously,⁹⁻¹² in respect to various aspects of the cycle, including changes of the relative length of the Q-T interval. Bazett,¹³ contrary to our findings, found that the Q-T segment was relatively decreased in length on *active* change of posture from the recumbent to the erect position. The formulas (mentioned heretofore) all assume that the Q-T will vary inversely with some function of the heart rate. This seems to be one instance in which the rate varies, but the Q-T remains practically the same.

SUMMARY

In the passive change of posture from the recumbent to the 60° head-up position, the relative value of the Q-T interval was very markedly increased in one case, moderately increased in four, and slightly increased in four; in one case, there was no significant change. This appears to be a transient, functional phenomenon, probably of neurogenic (sympathetic-parasympathetic) origin.

It is suggested that Q-T cal. can be used as a convenient designation to express the fact that the Q-T interval has been calculated for the physiologic variables: heart rate, age, and sex according to any one of the several formulas proposed for this purpose.

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Clinical Reports

DEATH FOLLOWING CORONARY THROMBOSIS IN A YOUNG WOMAN NINETEEN YEARS OF AGE

CASE REPORT WITH AUTOPSY FINDINGS

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A SEVERE degree of arteriosclerosis of the coronary arteries is rare in the first two decades of life. Zacks,¹ in his review of the pertinent literature, was able to find five cases of medial coronary sclerosis (and presumably infarction) in infants, and eight cases of coronary thrombosis in persons 10 to 20 years of age. To this latter group must be added Zacks' case and the case report by Jukl and Greenstein,² making ten in all. These cases were all men.

In so far as we are aware, the case presently to be reported is the first recorded instance of myocardial infarction in a woman under 20 years of age. White, Glendy, and Gustafson³ have reported the case of a woman 22 years of age who survived acute myocardial infarction during pregnancy; coronary embolism was considered to be a remote possibility. The case of a still younger female has been reported by May.⁴ His patient was 20 years of age and presented the clinical and electrocardiographic findings of acute infarction of the heart.

CASE REPORT

M. E. W., a young married woman 18 years and 11 months of age, entered the Naval Air Station Dispensary March 5, 1945, complaining of weakness. The family history disclosed nothing of medical significance. There was no past history of rheumatic fever, chorea, diphtheria, or tonsillitis. The patient stated that she had suffered from scarlet fever at 3 years of age but that there had been no complications. Thereafter, she remained well and healthy until three years before admission when there was a sudden onset of paralysis of the left lower portion of the face of unknown cause. Recovery from this disorder was complete in approximately one month. Urinalysis at that time showed albumin. The blood pressure was not taken.

Shortly after marriage (eight months prior to our examination), she experienced copious vaginal bleeding which ceased without treatment. Following this episode, there was progressive

The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department, or the naval service at large.

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loss of strength and appetite and she began to complain of severe headaches. However, it was not until three months before admission to the dispensary that she consulted a physician and was found to have high blood pressure. The treatment prescribed afforded some relief but did not abolish the symptoms.

Physical examination on admission revealed a frail, anxious person with moderate facial pallor. She was 5 feet, 4 inches in height and weighed 97 pounds. The temperature, pulse rate, and respirations were normal. The heart was found to be slightly enlarged. The sounds were of good quality except for accentuation of the aortic second sound. A slight systolic murmur was heard over the mitral area, but was not widely transmitted. The cardiac rhythm was regular at a rate of 86 per minute. The blood pressure was found to be 190/110. Examination of the ocular fundi showed the arteries to be contracted and irregular in size; there was arteriovenous nicking but no hemorrhages were seen. The peripheral arteries were soft. The remainder of the examination, including the neurological and psychologic aspects, revealed no definite abnormality.

The results of the laboratory studies were as follows: the erythrocyte count was 4.9 million per cubic millimeter; the hemoglobin was 102 per cent (Salhi); the leucocyte count was 7,850; and the differential was normal save for 6 per cent eosinophiles. Urinalysis showed 2 plus albumin, 6 to 8 white blood cells, and rare red blood cells per high power field. The erythrocyte sedimentation rate was normal, and the Kahn test was negative.

A diagnosis was made of essential hypertension and of hypertensive heart disease. The following additional studies were carried out, partly with the view of determining the patient's suitability for sympathectomy.

The basal metabolic rate was plus twenty. The electrocardiogram (Fig. 1), taken four days after entry shows complete A-V dissociation with an auricular rate of slightly over 100 and a ventricular rate of 50 per minute. In all other respects, the record is within normal limits save for rather low but upright T waves in Lead I and inverted (triphasic) T waves in Lead IVf. Tele-roentgenogram of the chest revealed slight cardiac enlargement and slight prominence of the great vessels; the lung fields were clear. Intravenous pyelogram revealed no definite abnormality. Nine grains of sodium amytal were administered during the course of four hours with no significant reduction in blood pressure. A Mosenthal renal function test was carried out and was considered to show borderline impairment of renal function.

Following the completion of the studies, the patient was advised to take a small amount of one of the barbiturates and was urged to enter a civilian clinic for further study.

Nothing more was heard from the patient until May 14, 1945, ten weeks after she was first seen. At noon, while walking slowly, she experienced moderate pain in the arms extending down to the fingertips, but there was no pain in the substernal or precordial areas. This was accompanied by a sensation of weakness, sweating, nervousness, and palpitation. Within three hours of the onset of these symptoms, she was seen by one of us (W. F. E.) at which time her symptoms had almost subsided. Examination revealed the temperature to be normal; the pulse rate, 78 per minute; and the blood pressure, 196/120. No cyanosis was observed. The rhythm of the heart was regular and the heart sounds were of good quality. No murmur or friction rub was heard. The lungs were clear.

She was advised to rest quietly at home. That evening she awakened from a nap much refreshed and when asked by her landlady how she felt, answered: "I feel fine and I think I'll eat some of that fried chicken you are cooking." With this the landlady walked out of the room, but hurried back when she heard a "gurgling" sound, and found that the patient had died.

Autopsy.—Permission was granted for an autopsy limited to the heart, kidneys, and adrenals.

The aorta was smooth and elastic along its entire length except for numerous elevated atheromatous lesions, including plaques in the region of the coronary ostia.

The heart, the proximal 15 cm. of the aorta, and a small attached portion of the pulmonary artery, trachea, and tracheal nodes weighed altogether 395 grams. The wall of the right ventricle measured approximately 5 mm. in thickness, and the wall of the left ventricle, 2 centimeters.

In the endocardium of the right ventricle, 5 mm. below the attachment of the posterior commissure of the tricuspid valve, there was a smooth white area of superficial thickening. Five

millimeters below this there was an area of fibrosis about 2 mm. in diameter. The posterior papillary muscle showed a well-defined area approximately 1×0.5 cm. which was white and smooth, and which on sectioning appeared to be endocardial thickening or superficial fibrosis. The valves showed no lesions.

Multiple cross sections through both coronary arteries revealed marked thickening of the walls and narrowing of the lumen. The right coronary orifice was narrowed. The right coronary artery appeared to be completely occluded by a thrombus approximately 4 cm. from its origin. The lumen of the left coronary artery, 1.0 cm. from its origin and just proximal to the origin of its circumflex branch, was reduced to a narrow slit by atherosclerosis.

Sections of the posterior wall of the right ventricle, taken through the areas described, showed hypertrophied muscle fibers interspersed with extensive connective tissue hyperplasia and replacement fibrosis, the continuity of muscle fibers being lost by intervening fibrous tissue.

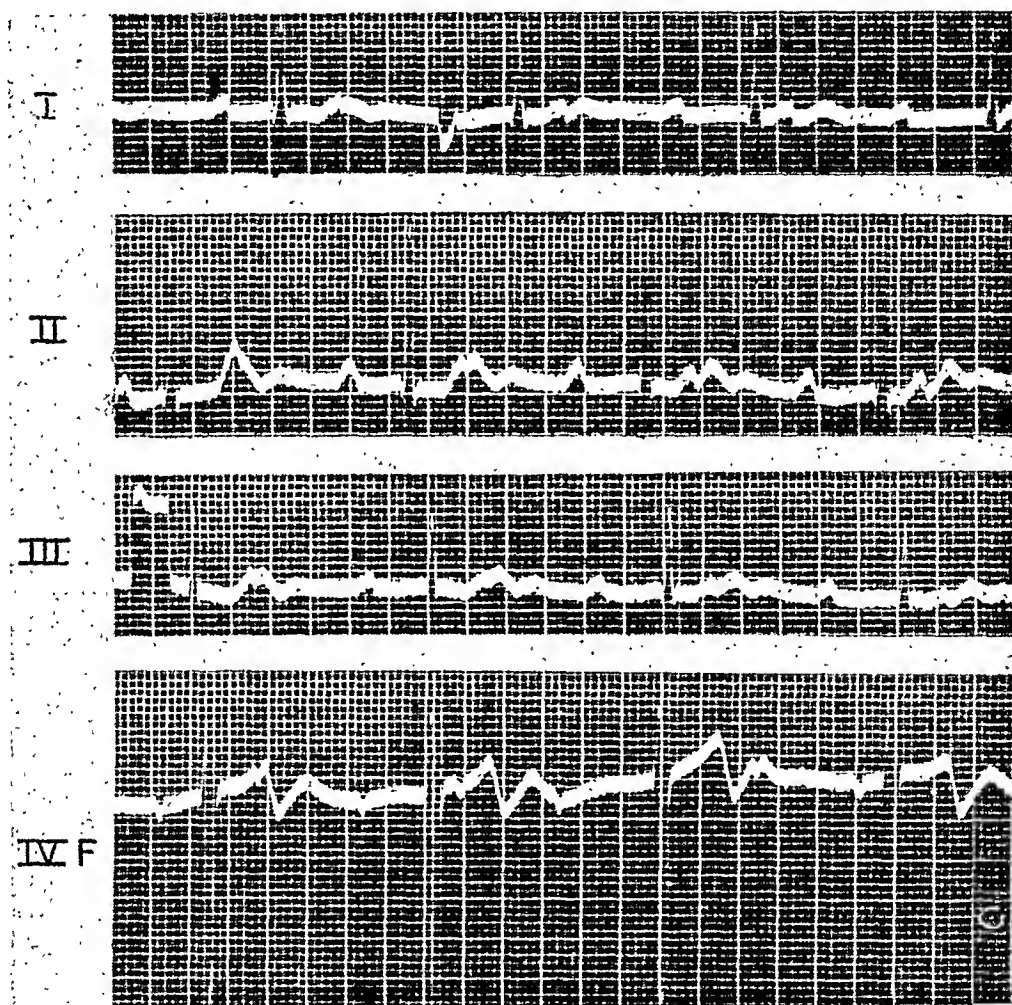


Fig. 1. —Electrocardiogram taken ten weeks before death, showing complete A-V dissociation in the case of a woman 19 years of age, who died following coronary thrombosis.

In a section of the anterior wall of the right ventricle the changes were most striking in the epicardial tissue, which showed proliferation of the endothelial surface of the visceral pericardium, edema, and infiltration by diffusely scattered lymphocytes.

The anterior wall of the left ventricle, in a section taken through the base of the septum, showed fibrosis similar to that described in the contiguous portion of the right ventricular wall. The most extensive area of fibrosis was just beneath the endocardial surface which was involved in focal lymphocytic infiltration, beneath which there was an area of hyaline necrosis.

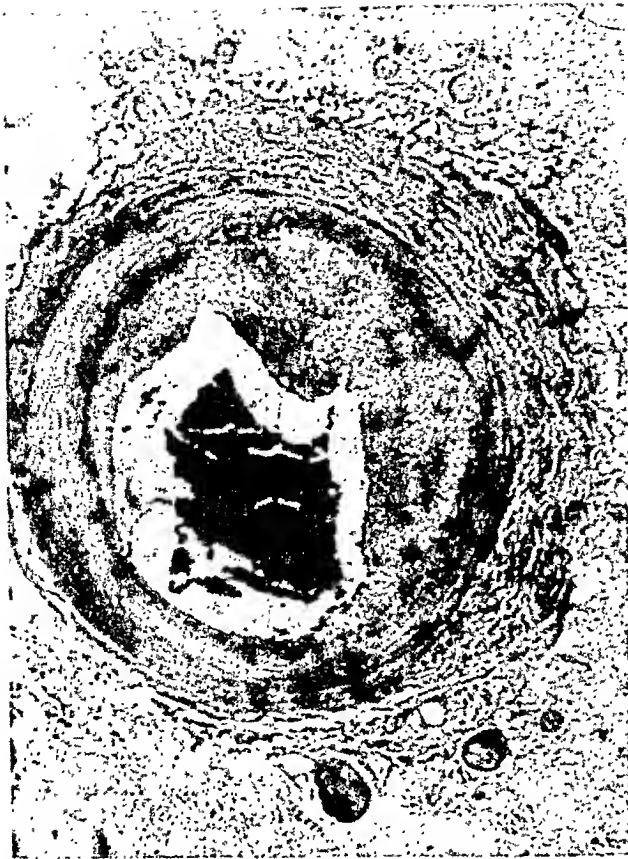


Fig. 2.—Microphotograph of section of right coronary artery, showing clot still partly adherent to lumen

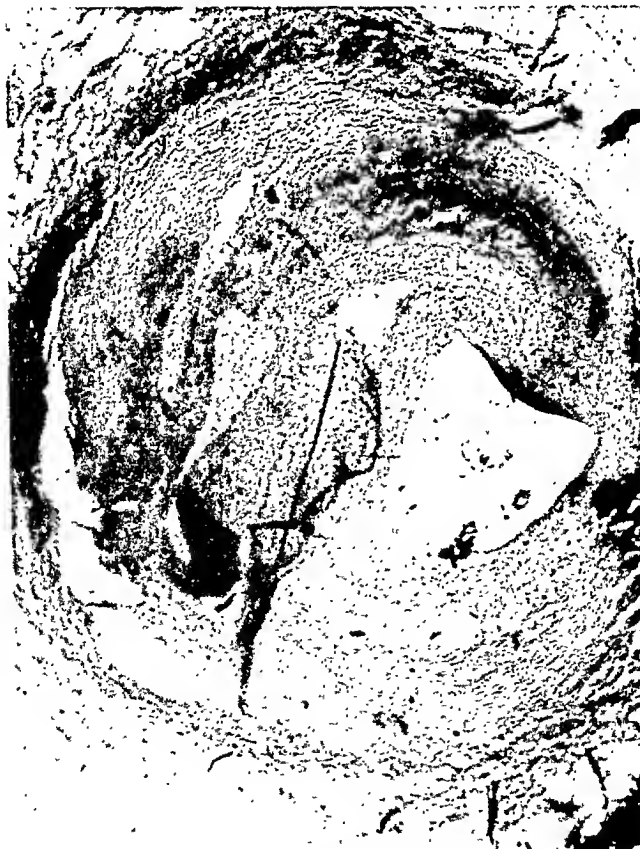


Fig. 3.—Microphotograph of section of left coronary artery, showing marked atherosclerotic changes of the intima.

Sections of the right coronary artery taken from 4 to 5 cm. from its origin (Fig. 2) showed that the lumen was eccentrically narrowed by irregular elevations of the endothelium, which had a frayed appearance showing loss of cell structure, and foci of necrosis beneath which there were deposits of lipoid and fatty globules. There was marked cellular infiltration of the media and sub-intima by lymphocytes, plasma cells, and a smaller number of polymorphonuclear leucocytes. A fresh thrombus occluded the small, distorted lumen.

A section of the left coronary artery, 1 cm. from its origin (Fig. 3), showed thickening of the vessel wall with distortion and narrowing of the lumen. The endothelial surface was interrupted by irregular elevations characterized by subendothelial collections of lymphocytes and surface deposition of fibrin and clumps of erythrocytes. Beneath these areas, cholesterol crystals, hyaline degeneration, and two foci of necrosis were seen.

The wall of the ascending aorta, in a section taken just below the arch, showed proliferative and degenerative changes in the intima characterized by hyaline necrosis and cholesterol deposits. In the adventitia, the perivascular tissue around the vasa vasorum showed collections of large mononuclear cells, unusually large plasma cells, and small areas of hyaline or fibrillary appearance.

In the kidney, several small foci of lymphocytic infiltration were found in the cortex, located just beneath the capsule, and associated with fibrosis or hyalinization of the glomeruli in immediate proximity. There was no diffuse fibrosis or degenerative change, the glomeruli of other portions showing normal histologic structure. The small vessels seen in the section showed no lesions.

A section of the adrenal showed the normal histologic structure.

SUMMARY

The history and autopsy findings have been presented in the case of a 19-year-old woman with hypertensive and coronary heart disease, who died following coronary thrombosis. The striking feature of the case is the age at the time of death. This is the first recorded instance, as far as we know, of a woman under the age of 20 years with this disorder.

There was no evidence of rheumatic fever, diabetes, or xanthomatosis, factors which may be responsible for the precocious development of arteriosclerosis or atherosclerosis. However, the arterial hypertension almost surely was an important etiologic factor in this regard. The cause of the hypertension was not determined. It was not secondary to coarctation of the aorta, polycystic kidney disease, nephritis, aberrant renal artery, or tumor of the adrenal gland.

Complete A-V heart block was present at the time one of the examinations was carried out. It can be readily explained on the basis of impaired blood supply to the specialized conduction tissue. The fact that it was present only as a temporary phenomenon suggests that rather dramatic changes in blood supply to the conduction tissue occurred during the period prior to the terminal events.

We are indebted to Lieutenant Commander Eleanor W. Townsend, Medical Corps, United States Naval Reserve, pathologist, U. S. Naval Hospital, Pensacola, Fla., for the pathologic findings in this case, and to Dr. William B. Porter of the Medical College of Virginia for taking the microphotographs.

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PERICARDIAL EFFUSION DUE TO HEMOLYTIC STREPTOCOCCUS FOLLOWING AN ACUTE UPPER RESPIRATORY INFECTION; ASSOCIATED PLEURAL EFFUSIONS

REPORT OF CASE AND REVIEW OF LITERATURE

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THERE have been an increasing number of reports¹⁻⁸ of the association of acute pericarditis, with or without effusion, with an acute upper respiratory infection. However, the isolation of the hemolytic streptococcus from the pericardial effusion in this syndrome is unusual and prompted this report.

CASE REPORT

W. J., a 52-year-old white taxicab driver, became ill in the first week of August, 1946, with the onset of a sore throat accompanied by chills and a feverish feeling. For the following three weeks the patient medicated himself with aspirin, saline gargles, and topical argyrol. Because of continuation of the sore throat and fever, he consulted a physician on Aug. 22, 1946, who found an exudative, bilateral, follicular tonsillitis with bilaterally tender and enlarged anterior cervical glands. Because of distant heart sounds, an x-ray film was made. This revealed an enlarged cardiac shadow, which was interpreted as being due to a pericardial effusion (Fig. 1).

The patient was put on oral penicillin, 100,000 units every four hours, which he continued to take until his admission to the hospital six days later; this was necessitated by the onset of increasing orthopnea and pain in the anterior part of the chest, both of which were relieved by assuming the upright position. He entered the hospital on Aug. 28, 1946. Further questioning on admission did not reveal a previous history of rheumatic fever, heart disease, malaria, or any of the enteric fevers. The patient stated that a week prior to the onset of his illness all of his family, including himself, drank some raw milk, but that he was the only one who became ill.

The physical examination revealed the patient to be well developed and nourished. He was dyspneic, orthopneic, and slightly cyanotic. The rectal temperature was 100° Fahrenheit. The pharynx was normal. There were no distended neck veins in the erect position. There was dullness on percussion and diminished breath and voice sounds on auscultation over the left lower lobe posteriorly. The heart was thought to be enlarged slightly to the left. The sounds were distant. No murmurs were heard. The radial pulse and ventricular rates were 80 per minute and regular. The blood pressure was 100/76. The spleen was felt 3.0 cm. below the costal margin on inspiration and was firm. The liver was not felt. No peripheral edema was present.

There were 7,600 white blood cells per c.mm., with 81 per cent neutrophils. The urine analysis showed a specific gravity of 1.020, the reaction was alkaline, there was no sugar nor albumin, and the microscopic examination was normal. The blood sedimentation rate was 50 mm. at the end of one hour. Roentgen examination of the chest on admission (Fig. 2) showed a moderate degree of pleural effusion at the left base and a slight enlargement of the cardiac sil-

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houette. The blood nonprotein nitrogen was 32 mg. per cent. The serum total protein was 7.46 Gm. per cent, with 4.33 Gm. of albumin, 3.13 Gm. of globulin, and an albumin-globulin ratio of 1.38. The venous pressure in the right antecubital vein was 120 mm. of water. The circulation times revealed an arm-to-tongue (calcium gluconate) time of 14 seconds and an arm-to-lung (ether) time of 6 seconds. Agglutination tests for typhoid, paratyphoid, typhus, and brucellosis were negative. The brucella skin test was negative after forty-eight hours. A blood culture was negative. An electrocardiogram (Fig. 3,A) showed the T waves to be inverted in Leads I and IV and diphasic in Lead II. The electrocardiogram was interpreted as being consistent with the diagnosis of pericarditis in the subacute or chronic stage.



Fig. 1.—Aug. 22, 1946 (six days before hospitalization). X-ray of chest shows enlarged cardiac silhouette due to pericardial effusion and obliteration of left costophrenic space.

Fig. 2.—Aug. 30, 1946 (third day of hospitalization). Note that the cardiac shadow has decreased considerably, but that the left pleural effusion persists.

The course in the hospital is shown in Fig. 4. During the first few days in the hospital, the dyspnea and orthopnea, so prominent on admission, practically disappeared only to recur on September 3, seven days after hospitalization. This was associated with a shaking chill and a temperature of 100.6° Fahrenheit. A blood culture was negative. Thoracentesis of the left pleural cavity was done on September 5, and 4.0 c.c. of a thick, light yellow, gelatinous fluid were evacuated. Both the culture and the smear of this fluid for acid-fast organisms were negative. On September 10, with the temperature at 102.8° F., the patient was started on intramuscular penicillin, 30,000 units every three hours day and night.

On September 12, a pericardial tap in the left fifth intercostal space anteriorly at the nipple line was performed and about 65 c.c. of a light yellow, thick, fibrinous fluid was obtained. The fluid had a specific gravity of 1.020 and contained many red and white blood cells. Of the white blood cells, 75 per cent were polymorphonuclear leucocytes and 25 per cent were lymphocytes. The protein content was 3.53 Gm. per cent. Culture yielded a pure growth of *Streptococcus haemolyticus*. Smear for acid-fast organisms was negative. A cell block showed a sediment made up of fibrin, red blood cells, leucocytes, and many large slightly eosinophilic cells containing one or more nuclei which tended to be rather large. Many of the nuclei had prominent nucleoli. No tumor cells were seen. Guinea pig inoculation was negative. The blood sedimentation rate at this time was 110 mm. at the end of one hour.

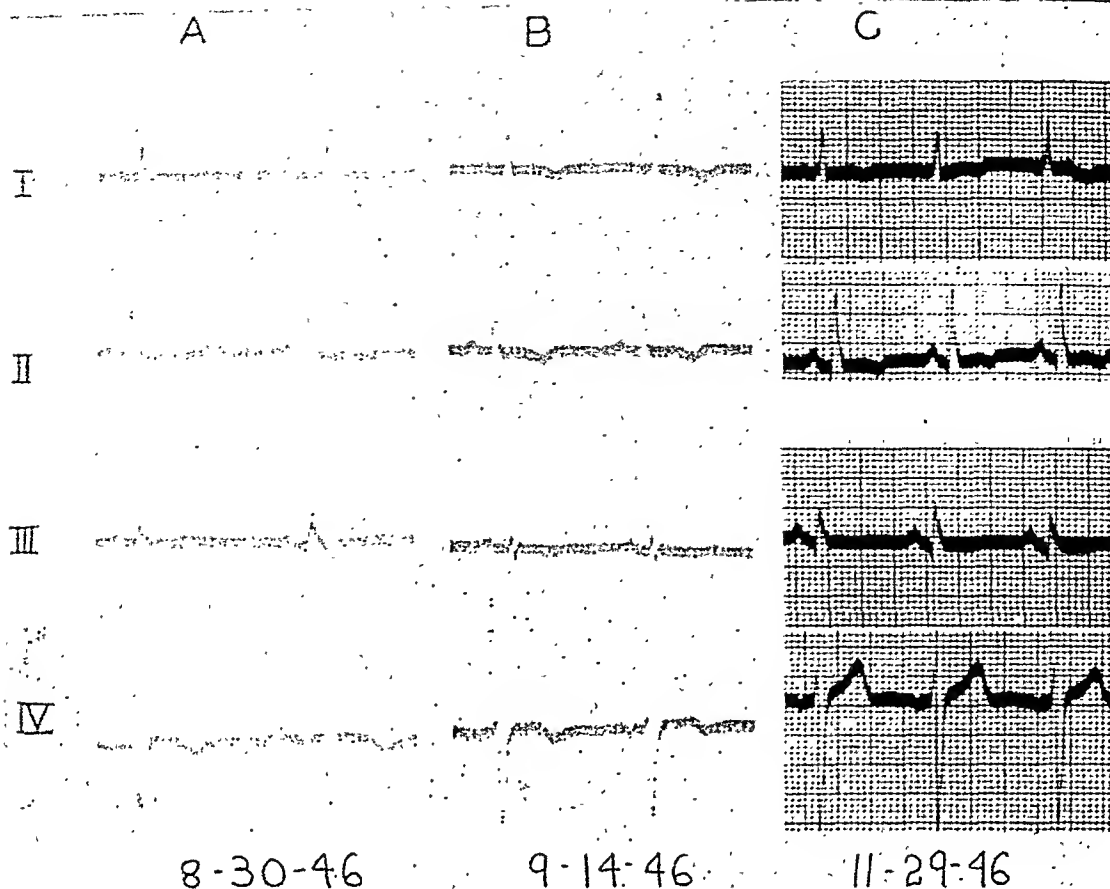


Fig. 3.—A, Electrocardiogram taken on third hospital day. T_1 and T_2 are inverted; T_3 is diphasic. B, Eighteenth hospital day; T_1 and T_2 are further inverted. C, Approximately one month after leaving hospital; T_1 and T_2 are still inverted, T_3 is now upright.

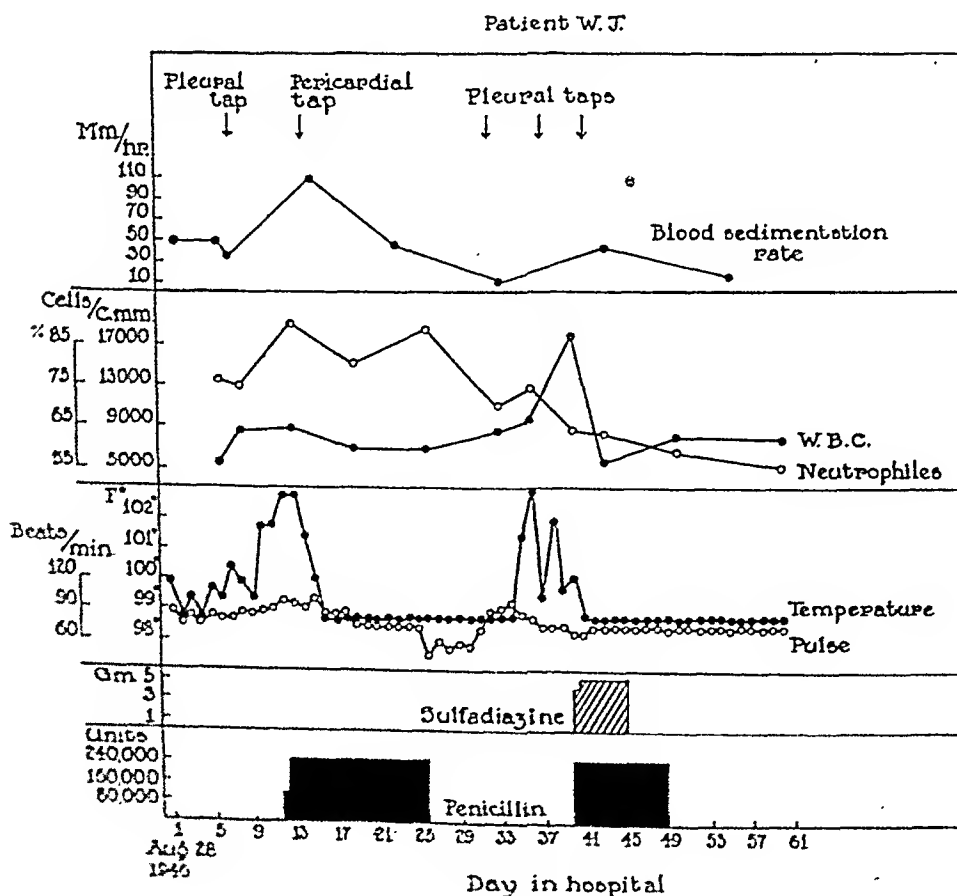


Fig. 4.—Chart of course in hospital.

Following this paracentesis, there was marked relief of the dyspnea and orthopnea. Six days later, this procedure was repeated with the purpose in mind of injecting air into the pericardial sac for roentgen confirmation of a pericardial effusion. However, despite needling at the same site as previously, no fluid was obtained. The penicillin was stopped on September 23 after a total of 3,060,000 units had been given in thirteen days. While the serial x-ray films (Figs. 5, 6, and 7) showed a decrease in the size of the cardiac silhouette, they also revealed a progressive increase in pleural fluid at the left base. Thoracenteses were done in the left eighth intercostal space posteriorly on September 28, October 3, and October 7. At the first thoracentesis, 220 c.c. of a straw-colored fluid with a specific gravity of 1.020 and a total protein of 3.35 Gm. per cent were obtained. The fluid was cultured and a smear examined for acid-fast organisms. Both were negative. The second chest tap produced 900 c.c. of a bloody fluid with a total protein of 3.06 Gm. per cent, which was negative on culture and for acid-fast organisms. A cell block revealed no tumor cells. An inoculated guinea pig showed no evidence of tuberculosis. The third tap was productive of 600 c.c. of bloody fluid with a total protein of 3.41 Gm. per cent. Culture of the fluid and smear for acid-fast organisms was negative.

An electrocardiogram taken on September 14 (Fig. 3,B) showed further inversion of T_1 as well as of T_2 , as compared with the admission graph (Fig. 3,A).

On October 2, there was another rise in temperature to 102.6° F., accompanied by a recurrence of the dyspnea and orthopnea. A pleuropericardial friction rub was heard in the left fifth intercostal space anteriorly at the level of the nipple. The white blood count rose to 17,700 cells per c. mm., with 63 per cent neutrophils. The blood sedimentation rate was 40 mm. at the end of one hour. Intramuscular penicillin, 30,000 units every three hours day and night, and oral sulfadiazine, 5.0 Gm. daily, were started on Oct. 7, 1946. The temperature was normal by the next day. Sulfadiazine was discontinued after 29 Gm. had been given because of the appearance of crystals in the urine. The penicillin was stopped on October 16 after 2,400,000 units had been given in ten days.

By October 24, the patient had improved sufficiently to be discharged. The spleen was still palpable and there was minimal effusion at the base of the left lung. The blood sedimentation rate was 17 mm. at the end of one hour. The white blood count was 7,500 cells per c. mm. with 55 per cent neutrophils.

The patient was re-examined on November 29. He had no complaints. The lungs were clear to percussion and auscultation. The heart was not enlarged and the sounds were good. The radial pulse and ventricular rate were 80 per minute. The spleen was felt about 0.5 cm. below the costal margin on deep inspiration. There was no enlargement of the liver and no peripheral edema. An x-ray of the chest (Fig. 8) showed the heart to be normal in size and the lungs to be clear. The electrocardiogram (Fig. 3,C) still showed inversion of T_1 and T_2 , but T_4 had become upright.

COMMENT

Although reports on the association of an upper respiratory infection with an acute pericarditis (with or without concomitant effusion) are becoming more numerous, the isolation of a definite etiological agent in these cases is still unusual. Gardner¹ obtained complete recovery by treating with Prontylin one patient with a hemolytic streptococcus pericarditis which followed a pharyngitis and tonsillitis. This was the only reported instance in which this organism was cultured from the pericardial fluid. Willis² and Levine⁴ infer that the streptococcus found in the throat may have been the causative agent for the pericarditis in their cases, but describe neither taps nor cultures to substantiate this point.

Nathan and Dathe⁷ report eight cases as instances of respiratory infection and pericarditis. Five patients had an associated pericardial effusion and, on paracentesis, four of these were found to be hemorrhagic. Culture, smear, and guinea pig inoculation of the fluid yielded no organisms. In one patient there



Fig. 5.

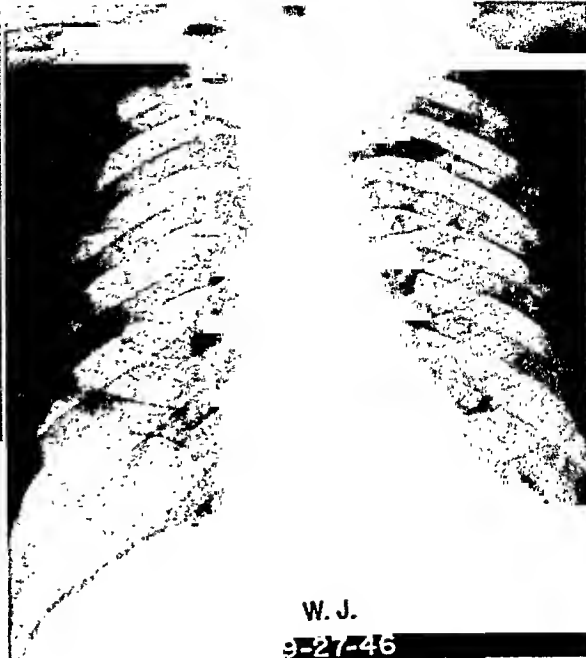


Fig. 6.

Fig. 5.—Sixteenth day of hospitalization. Note bilateral pleural effusions.

Fig. 6.—Thirty-first hospital day. Cardiac shadow is normal in size. Fluid at left base still present.

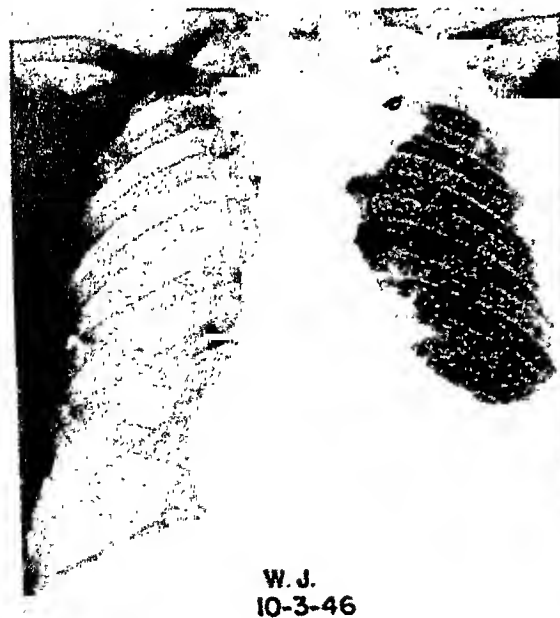


Fig. 7.

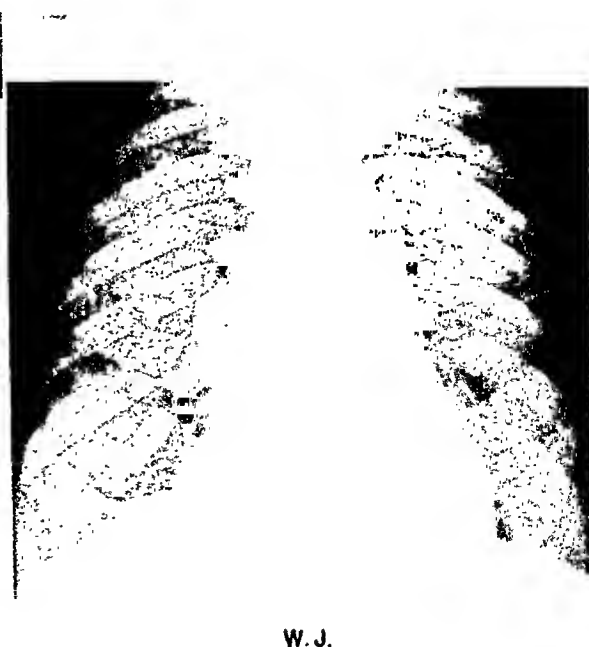


Fig. 8.

Fig. 7.—Thirty-seventh hospital day. Note marked increase in left pleural effusion. Thoracentesis evacuated 900 c.c. of hemorrhagic fluid.

Fig. 8.—Approximately one month after discharge from hospital. X-ray of heart and lungs is normal.

was an associated pleural effusion. The peripheral white blood count varied between 6,000 and 27,400 cells per cubic millimeter. They postulate that involvement of the pericardium may occur by spread from the contiguous hilar lymph nodes or by a hypersensitive response of the pericardium to an offending organism, the immune reaction of the body being inadequate.

Nay and Boyer⁵ review fifteen cases of acute pericarditis in which the etiology was undetermined. The existence of an associated upper respiratory infection is not definitely stated. None of these patients had any past or present history of rheumatic fever. In ten patients, there was a pericardial effusion. In twelve instances, the onset of the pericarditis was extremely abrupt, with sudden severe precordial pain and usually with chills and fever. The pain was aggravated by deep respiration, and by twisting the trunk and by swallowing. Leucocytosis was exceptional; only four patients had white counts above 9,000 cells per cubic millimeter. These counts were 12,000, 21,000, 16,000, and 33,000 cells, respectively. Fourteen patients had electrocardiographic evidence suggestive of pericarditis.

Smalley and Ruddock⁸ report three cases of pericarditis following pharyngitis. One case is reported in detail. Three pericardial paracenteses yielded a total of 1,870 c.c. of a cloudy yellow fluid but in none was a positive culture obtained. The patient was treated successfully with 3,840,000 Oxford units of penicillin parenterally.

Hall⁹ in 1925 cured a patient with intravenous mercurochrome after a hemolytic streptococcus (isolated from the blood stream) had resulted in an acute pericarditis. There was no concomitant effusion, so that no culture was taken directly from the pericardial sac.

The course of events in our patient's illness would then seem to be as follows: his illness started with tonsillitis. Although we have no cultural proof, we strongly suspect that the tonsillitis was the result of streptococcal infection since Rantz, Boisvert, and Spink¹⁰ have shown that the combination of exudative tonsillitis and pharyngitis with tender anterior cervical glands permits the diagnosis of a hemolytic streptococcus infection with a high degree of accuracy, even without a bacteriologic study of the flora of the throat. Within three weeks, a pericarditis with effusion had occurred which necessitated hospitalization. Culture of the pericardial fluid on one occasion yielded a pure growth of hemolytic streptococcus. The course was complicated by left pleural effusion which was repeatedly sterile. Two courses of parenteral penicillin were necessary to combat the infection. The success with penicillin is not unexpected.¹¹

The electrocardiographic picture (Fig. 3) is compatible with pericardial involvement in the later stages.¹² Young⁶ and Rantz, Spink, and Boisvert¹³ have shown; however, that similar electrocardiographic findings may occur with upper respiratory infections in the absence of clinical pericardial involvement.

SUMMARY

1. A case is presented of a 52-year-old man with pericardial and pleural effusion which followed an acute upper respiratory infection. Culture of the

pericardial fluid yielded a hemolytic streptococcus. Treatment with penicillin was successful.

2. The literature is reviewed, and the rarity of isolation of the hemolytic streptococcus from the pericardial effusion in such cases is stressed.

ADDENDUM

The patient was last seen on Oct. 22, 1947, a year after discharge from the hospital. The heart was normal in size. Blood pressure was 150/90. The spleen was no longer palpable. The electrocardiogram showed T_1 and T_2 to be upright, though low.

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INTERATRIAL SEPTAL DEFECT ASSOCIATED WITH SYPHILITIC AORTIC INSUFFICIENCY

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A RECENT post-mortem study has clarified an apparent clinical inconsistency and has revealed to us a combination of cardiac lesions which may be diagnosed prior to death. Syphilitic aortic insufficiency, coexisting with a large interatrial septal defect, was demonstrated in one case. The files of over 30,000 autopsies performed from 1929 to 1946 at the Los Angeles County Hospital contained only one other case of a similar nature.

The physical signs, when associated with the electrocardiograms and roentgenograms, are fairly distinctive.

There are several excellent articles which are quite complete reviews of the literature in regard to interatrial septal defect and associated acquired valvular lesions. McGinn and White¹ in 1933 presented and summarized the clinical and pathologic findings in twenty-four cases showing the combination of mitral stenosis and interatrial septal defect. Roesler² in 1934 reviewed sixty-two cases illustrating the clinical and anatomic peculiarities of interatrial septal defects. In at least three-fourths of these cases, valvular lesions were found which affected predominately the mitral orifice. There was no case with an isolated definite aortic regurgitation associated with the septal defect present in his series. Tinney³ in 1940 reported two autopsied cases of uncomplicated interatrial septal defect. He also reported on twenty-two others gleaned from the literature since Roesler's review. He found that 68 per cent of the twenty-two cases had chronic valvular lesions. In one-half of these the lesion was mitral stenosis. Burrett and White⁴ in 1945 presented a clinical analysis of comparative studies in the sixty-two cases collected by Roesler and thirty-one autopsied cases collected since that date. Certain criteria for the recognition of uncomplicated interatrial septal defect, as well as for the recognition of the septal defect associated with mitral stenosis, were presented. Mitral stenosis was found in nineteen of the thirty-one cases.

The association of syphilitic aortitis, mitral stenosis, and interatrial septal defect was reported by Kirshbaum and Perlman⁵ in 1939. As the patient died on admission to the hospital, there was no time for a clinical study of this case. With this exception, the literature contains no report which the author could find associating interatrial septal defect with aortic insufficiency on a syphilitic basis.

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In keeping with the established criteria as presented by several of the authors here noted, the files of the Los Angeles County Hospital were searched for cases of interatrial septal defect. Twenty-three cases were found in which the defect was greater than 1.0 cm. in diameter and in which no other congenital cardiac anomaly was present. All patients in this series were older than one year of age. Of these, nine had an associated mitral valvulitis. Only two patients had aortic incompetence due to syphilitic aortitis. The latter two cases form the substance of this report.

CASE REPORTS

CASE 1.—F. M., a 60-year-old Mexican farmer, first entered the Los Angeles County Hospital on Feb. 16, 1945, because of pain in the precordium which was aggravated by eating a heavy meal and by exercise. He also had ankle edema during the day. These symptoms had been present

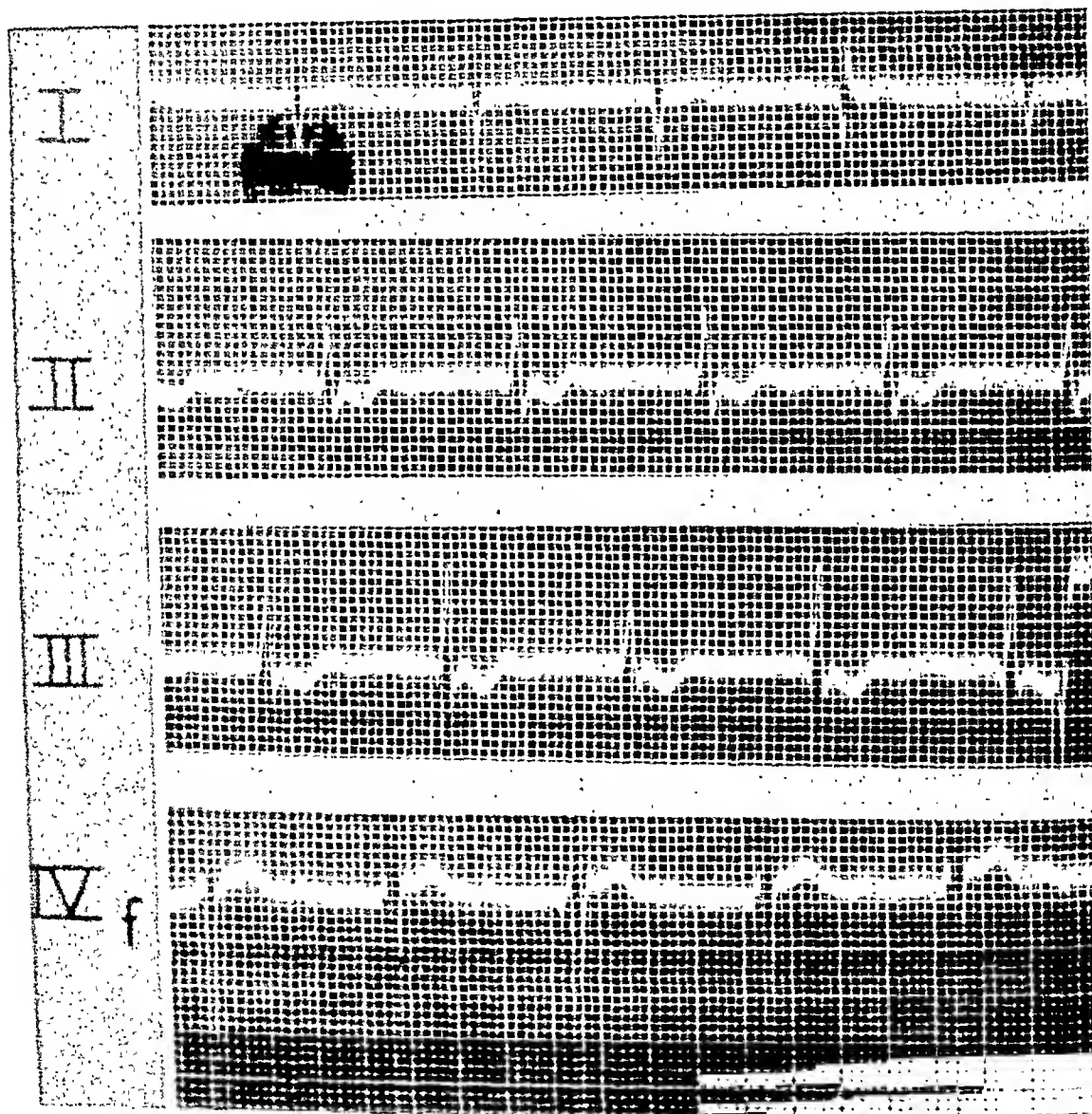


Fig. 1.—Case 1. The electrocardiogram shows right axis deviation, auricular fibrillation, and digitalis effects.

for only a few weeks. A summary of the past history revealed that his blood Wassermann was positive in 1937 and 1938. He received a course of twenty-four intravenous and twelve intramuscular injections. The patient was discharged on March 9, 1945, on a cardiac regimen. He was followed both in the hospital and in the outpatient clinic until his death on Sept. 15, 1946. His last admission to the hospital was on Sept. 10, 1946, when he entered in severe congestive heart failure.

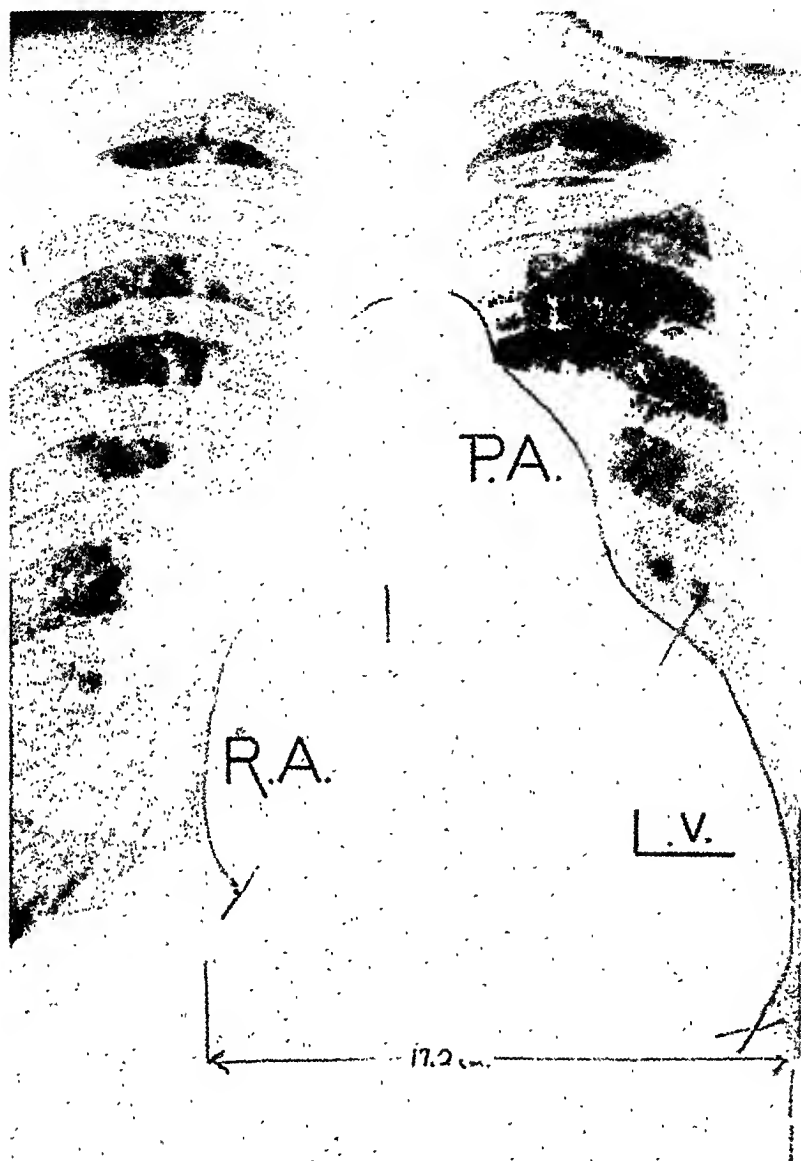


Fig. 2.—Case 1. The frontal view of the teleroentgenogram shows the markedly dilated pulmonary artery with very prominent hilar markings. P.A., Pulmonary artery; L.V., left ventricle; R.A., right atrium.

Physical findings were quite similar on each admission and are summarized. The blood pressure was 160/45. The patient was well developed and well nourished. He was orthopneic and had pitting edema of both ankles. The carotid pulsations were accentuated and a venous pulse was noted. In the lungs, there were a few fine basal râles bilaterally. The heart was enlarged to the anterior axillary line in the sixth intercostal space. The cardiac rate was 120 per minute and was irregular. A loud to-and-fro murmur was heard at the aortic area and in the third left intercostal space at the left sternal border. At the apex was a longer and lower-pitched systolic murmur. There was no diastolic murmur heard at the apex. The liver was palpable three fingerbreadths below the right costal margin. The extremities revealed pitting ankle edema.

The electrocardiograms all showed right axis deviation. The latest electrocardiogram was taken in March, 1946. This tracing showed auricular fibrillation, right axis deviation, and digitalis effect (Figs. 1). The teleroentgenograms revealed a markedly enlarged heart with both right and left ventricular hypertrophy. The transverse diameter of the heart measured 17.2 cm., which is 43 per cent over normal according to the Hodges-Eyster⁶ correlation. The pulmonary artery was considerably dilated. The lung fields showed prominent hilar shadows with marked accentuation of the vascular pattern (Fig. 2). The blood Wassermann and Kahn tests were positive.

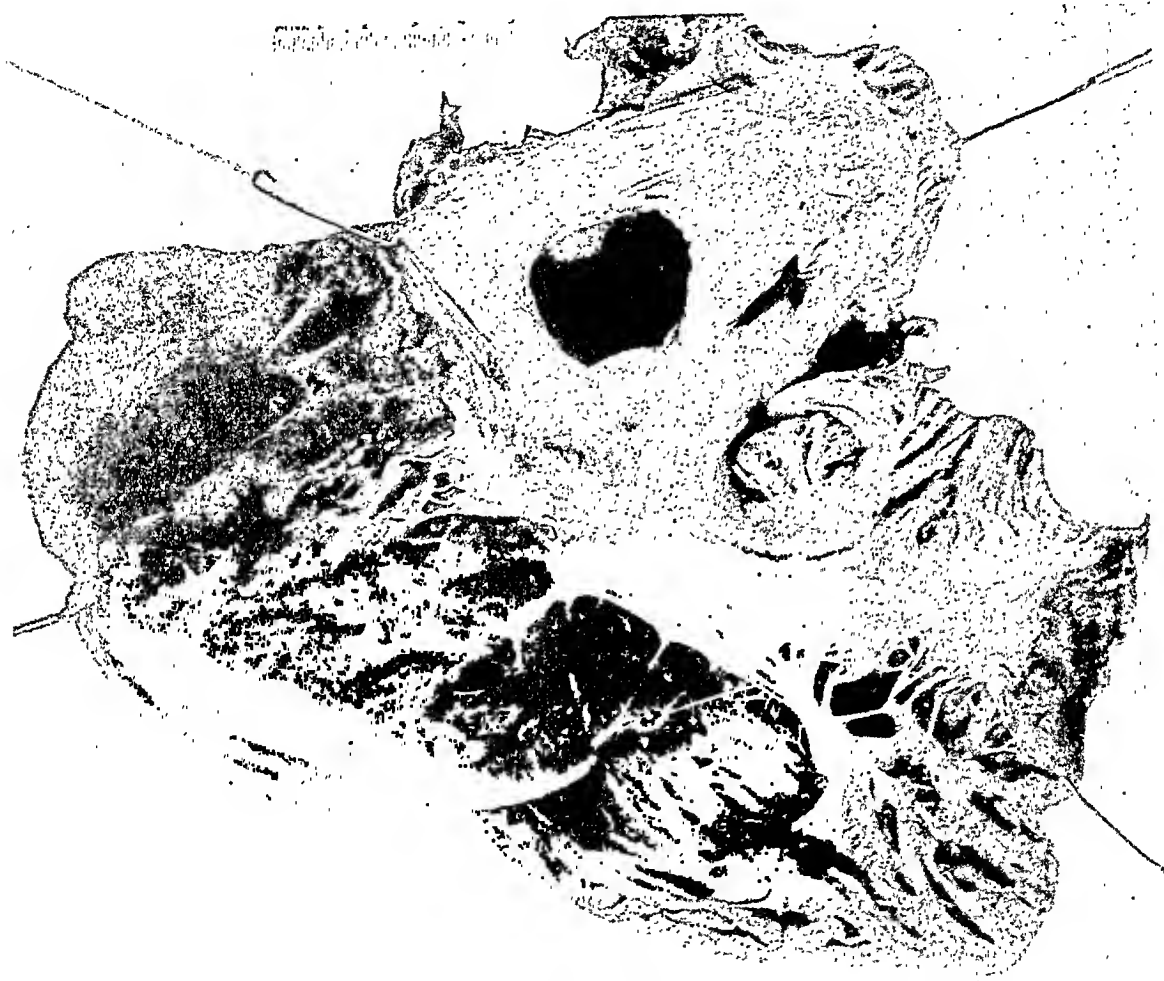


Fig. 3.—Case 1. The large interatrial septal defect is seen from the right side of the heart. Note the marked right ventricular hypertrophy.

Pathologic Findings: The post-mortem examination revealed the body of a 60-year-old Mexican man, which weighed 45.3 kilograms and measured 155 cm. in length. It was well developed and well nourished. There was pitting edema of the ankles.

The pericardium was slightly thickened and was adherent to the base of the aorta in its upper portion. The pericardial sac contained about 50 c.c. of a light amber-colored fluid. The heart was enlarged and weighed 700 grams. Both ventricular chambers were dilated. The aortic valve cusps were shrunken and deformed. The commissures of the cusps were separated and thickened. The free margins were moderately thickened and the base of the aorta was very rigid. The aortic ring measured 7.5 cm. in circumference; the valve was incompetent. The pulmonary valve ring was dilated and measured 9 centimeters. The pulmonary artery distal to the valve ring was 12 cm. in circumference. The mitral valve measured 11 cm. and the tricuspid valve

measured 15 centimeters. The ostia of both the right and left coronary arteries were markedly stenosed and admitted only the tip of the small point of the scissors and measured less than 1.0 mm. in diameter. The coronary arteries distal to the ostia, however, were quite wide and patent throughout, with only a very minimal amount of atherosclerosis. The interatrial septum contained a large defect which measured 3.5 cm. in diameter (Fig. 3). This defect appeared to be congenital in origin. The margins were smooth and the defect was located in the lower part of the septum. In the right atrium there were a few firmly adherent, small ante-mortem thrombi.



Fig. 4.—Case 1. The syphilitic aortitis is seen together with the hypertrophied left ventricle. The stenosed coronary ostia can scarcely be seen just above the deformed aortic valves.

Both atria were considerably dilated, the right more than the left. The right ventricle was also very dilated. The myocardium was hypertrophied and there was diffuse scarring present. The left ventricular wall measured 17 mm. in thickness while the stretched right ventricular wall measured from 6 to 8 millimeters. The papillary muscles of both ventricles were hypertrophied. The ascending aorta measured 9.5 cm. in circumference and showed both longitudinal and transverse wrinkling, with numerous pearly plaques. There was fairly diffuse atheromatous change in the intima (Fig. 4). The descending aorta showed a moderate amount of atherosclerosis.

Microscopic sections of the aorta were diagnostic of syphilitic aortitis. Sections taken from the margin of the interatrial septal defect showed normal cardiac muscle without evidence of any inflammatory changes. The left ventricular wall showed diffuse fibrosis. Sections from the pulmonary artery were normal.

The anatomic diagnoses were: (1) Syphilitic heart disease due to syphilitic aortitis with insufficiency; (2) congenital heart disease with interatrial septal defect; (3) left and right ventricular hypertrophy; and (4) chronic passive congestion.

CASE 2.—M. C., a 67-year-old white woman, entered the Los Angeles County Hospital on Oct. 9, 1942, with ankle edema, palpitation, and moderate dyspnea. Although these symptoms had been present for four years, they had become much worse during the past three months. Since 1938, the blood Wassermann was known to have been positive. She had two courses of arsenicals and three courses of bismuth since that time. Digitalis also had been taken sporadically in the past four years.

The physical examination revealed an elderly woman in no acute distress. The systolic blood pressure was 170; the diastolic could not be accurately determined, since the sounds were heard to zero. The neck veins were moderately distended. The heart was moderately enlarged to the left. The apex was in the fifth intercostal space lateral to the mid-clavicular line. There were no thrills palpable. The rhythm was irregular and slow. There was a Corrigan pulse and "pistol shot" sounds were elicited over the large vessels. The pulmonic second sound was louder than the aortic second sound. There was a systolic murmur at the apex transmitted to the axilla. There was a diastolic blowing murmur present in the first intercostal space to the right of the sternum. It was also heard to the left of the sternum in the third and fourth intercostal spaces. There was dullness with impaired fremitus over the right posterior chest. Numerous moist râles were heard in both lungs. The liver was palpable four fingerbreadths below the right costal margin. There was pitting edema of both lower extremities.

The electrocardiogram showed auricular fibrillation, right axis deviation, and digitalis effects (Fig. 5). The patient expired before roentgenographic studies could be made. The blood Wassermann and Kahn were positive.

Pathologic Findings: The post-mortem examination revealed the body of a well-developed, fairly well-nourished white woman 67 years of age, which weighed 56.9 kilograms and measured 156 cm. in length. The pupils were dilated and equal. There was no trauma to the head or body. There was no palpable adenopathy. Edema of the ankles was present. A midline scar below the umbilicus was present.

The pericardium was smooth and glistening. The pericardial sac contained several cubic centimeters of clear yellow fluid. The heart within the chest cavity showed a markedly dilated pulmonary artery which almost completely hid the aorta. The enlargement of the heart was due primarily to the enlargement of the right atrium and right ventricle. The heart weighed 550 grams. The aortic valve measured 8 cm. in circumference and showed thickening and shortening of the margins of the cusps with separation of the commissures. There was marked tree-barking of the aorta just above the aortic valve. The mitral valve measured 8.5 centimeters. Calcific nodules were present in the endocardium of the valve. The chordae tendineae were not shortened or thickened. The left ventricular wall measured only 13 millimeters. The right ventricle was extremely dilated and hypertrophied and the stretched wall measured 6 millimeters. Although the left atrium appeared normal, the right atrium was considerably dilated. The pulmonary artery measured 11 cm. in circumference. The pulmonary valve and the pulmonary artery and its branches were widened throughout. There were atheromatous plaques present on the intimal surface of the branches. The tricuspid valve measured 16 centimeters. The foramen ovale was closed, but just superior to it there was a large defect which measured approximately 3 by 5 centimeters. The coronary ostium of the right coronary artery was only pin-point in size but the vessel throughout its length was not narrowed. The left coronary artery was normal in its course and distribution and was patent throughout. The myocardium was firm and brown in color.

The microscopic sections of the aortic valve showed the changes of syphilitic aortitis.

The anatomic diagnoses were: (1) Syphilitic heart disease due to syphilitic aortitis with insufficiency; (2) congenital heart disease with interatrial septal defect; (3) right ventricular hypertrophy; and (4) chronic passive congestion.

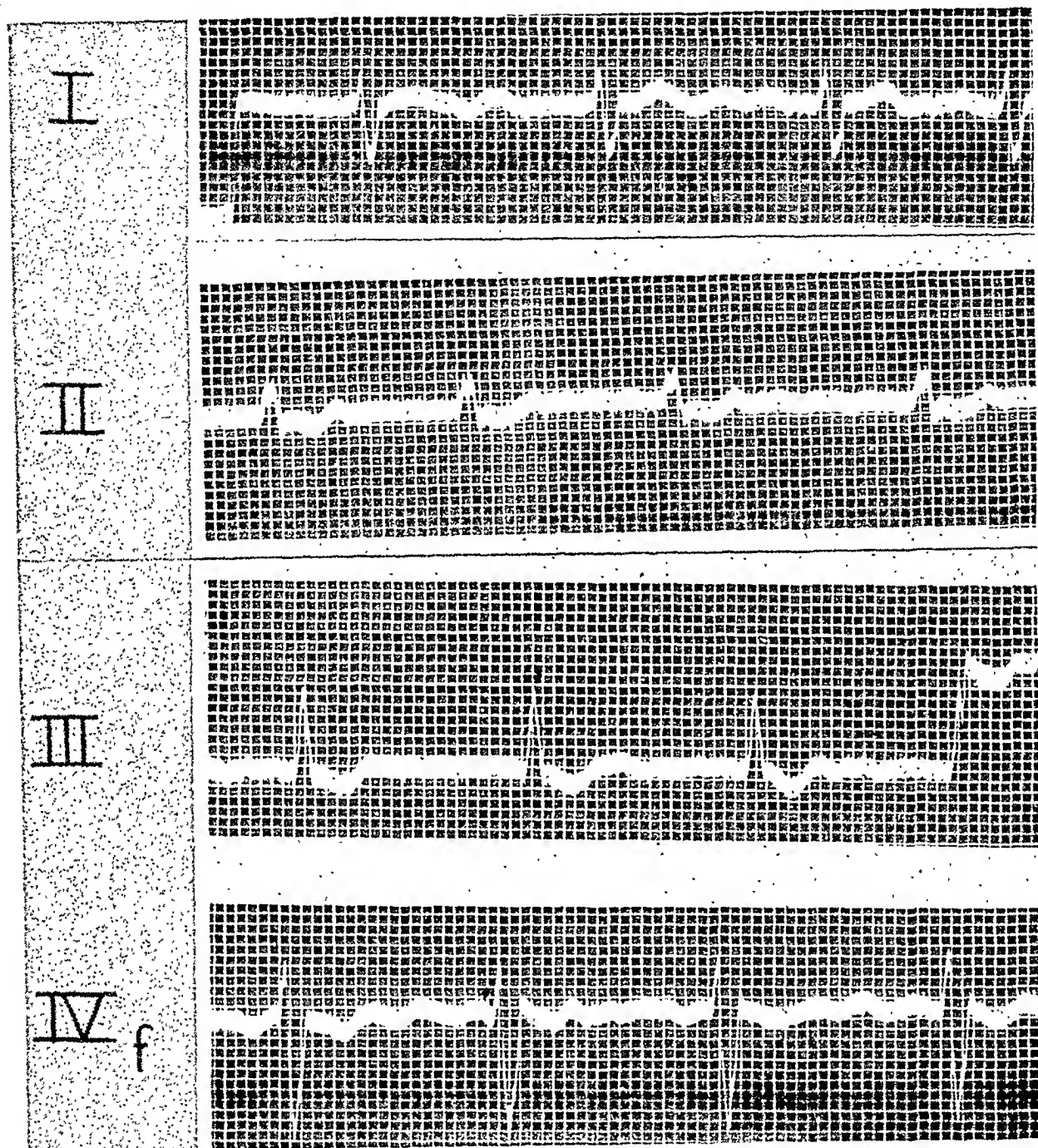


Fig. 5.—Case 2. The electrocardiogram shows right axis deviation, auricular fibrillation, and digitalis effects.

DISCUSSION

The clinical diagnosis in each of these cases was syphilitic aortic insufficiency with congestive heart failure. The clinical criteria which substantiated such a diagnosis were the usual findings of an enlarged heart, an aortic diastolic murmur, a Corrigan pulse with a very wide pulse pressure, and a history of syphilis with positive serology.

There were several inconsistent findings in both of these cases which made the given clinical diagnosis, by itself, untenable. The most apparent one was the presence of right axis deviation on all the electrocardiographic tracings in the presence of what appeared to be a free aortic regurgitation. Uncomplicated aortic insufficiency usually will cause left ventricular preponderance with left axis deviation. Auricular fibrillation is very uncommonly associated with syphilitic aortic regurgitation.⁶ Auricular fibrillation was evident from the electrocardiograms in both of these cases. Extreme dilatation of the pulmonary artery, as was seen from the roentgenograms in Case 1, does not fit in with the pathologic physiology of simple aortic insufficiency. The pulmonary artery in Case 2 was also very dilated and would undoubtedly have shown up on roentgenograms had they been taken.

From the foregoing, then, one should suspect that something more was present than uncomplicated syphilitic aortic insufficiency. The answer was found by the post-mortem studies already discussed. In both patients there was a large interatrial septal defect.

The embryology of defects of the interatrial septum are well described by Patten.⁸ Uhley⁹ has given an anatomic as well as a physiologic explanation for the right-sided hypertrophy in hearts with an interatrial septal defect. He has presented evidence to show that the interatrial septum normally lies horizontally when the body is erect. The left atrium is superior to the right atrium in the erect position. The force of gravity, then, even in an uncomplicated interatrial septal defect, tends to cause right atrial dilatation and hypertrophy. This phenomenon is accentuated when, for any reason, the left ventricle fails.

In a heart with a simple congenital interatrial septal defect, auricular fibrillation is not unusual.

Consequently, when the clinical diagnosis is syphilitic aortic insufficiency, but the electrocardiograms show right axis deviation and possibly auricular fibrillation and the roentgenograms of the chest reveal a very dilated pulmonary artery with increased hilar shadows, consideration should be given to the diagnosis of syphilitic aortic insufficiency complicated by an interatrial septal defect.

SUMMARY

1. Two cases of syphilitic aortic insufficiency associated with a large interatrial septal defect are presented.

2. The diagnosis of such a combination of lesions may be suspected before death when the clinical syndrome of syphilitic aortic insufficiency is associated with electrocardiographic evidence of right axis deviation and possibly auricular fibrillation, with roentgenographic findings of a distinctly dilated pulmonary artery.

I am grateful to Dr. E. M. Butt, Dr. E. M. Hall, and Dr. W. P. Thompson for helpful suggestions and comment. Also, I wish to thank Mr. A. J. Lonberg and Mr. L. Matlovsky for the photography.

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Abstracts and Reviews

Selected Abstracts

Booker, W. M., French, D. M., and Molano, P. A.: **Further Studies on the Acute Effects of Intra-abdominal Pressure.** *Am. J. Physiol.* 149:292 (May), 1947.

It has been shown that in all instances death can be produced sooner or later by maintaining an increased intra-abdominal pressure, which causes a circulatory failure produced from a venous stasis with consequent loss of plasma into the abdomen and the usual events to follow. It mattered not whether the air (used to increase the pressure) was introduced into stomach, intestine, or peritoneal cavity. A given pressure seems to cause an earlier circulatory failure and death in animals with small abdominal areas than the same pressure in animals of larger abdominal areas. Increasing the intra-abdominal pressure causes an increase in thoracic respiratory activity, most likely due to inactivity of the abdominal muscles. There is suggestive evidence that increased intra-abdominal pressure causes a damage to the myocardium which is ascribed to narrowing of the coronary arteries via the vagal pathways. The tendency of the QRS complex to return toward normal following sectioning of the vagi lends weight to this postulation.

BERNSTEIN.

Lee, R. E., and Lee, N. Z.: **The Peripheral Vascular System and Its Reactions in Scurvy: An Experimental Study.** *Am. J. Physiol.* 149:465 (May), 1947.

In the absence of information concerning the physiology of the peripheral vascular bed in scurvy, it was decided to make direct microscopic observations on the reactions of the smallest blood vessels in living scorbutic animals. The method used involves observation with the microscope of the mesenteric capillary bed in guinea pigs which are not under general anesthesia.

The dysfunction of the peripheral vascular apparatus in scurvy, as found, displays at least two prominent features: (1) A decreased responsiveness of the contractile elements, particularly of the arterial portion beyond the pulsatile small arteries, to epinephrine, with dilatation of these muscular vessels and a relatively sluggish flow of blood; and (2) A tendency of the terminal collecting venules, which drain the capillary bed, to become dilated and engorged and to rupture with trauma.

The response of the larger vessels (more than 100 to 150 micra in diameter) to topical epinephrine tests were within normal limits. At least 85 per cent of the petechiae were located in the small collecting venules which drain the capillary bed directly. In the scorbutic animals the capillaries were of the same diameter as those of the controls, and no abnormalities of the capillary wall were observed.

BERNSTEIN.

Sosman, M. C.: **Venous Catheterization of the Heart. I. Indications, Technics, and Errors.** *Radiology* 48:441 (May), 1947.

The author describes the technique used in the study of 100 patients by venous catheterization. There were thirteen failures in this series. These failures were attributed to venospasm which prevented proper propulsion of the catheter in two patients, to a defective catheter which did not have a proper curve and could not be properly guided in two instances; other

failures were attributed to kinking of the catheter at junction points in the venous system, to inexperience early in the series, and to lack of cooperation on the part of the patient. Ten autopsies performed on patients who succumbed to their disease or conditions unrelated to the procedure showed no trace of damage to the lining epithelium of the superior vena cava, right heart, nor pulmonary arteries.

The author used a number 9 French catheter made of radiopaque woven silk 100 to 125 cm. in length, with a single orifice at the tip. The catheter is flexible, yet sufficiently stiff that it can be twisted at its exposed end without buckling. The tip is slightly curved to facilitate its passage into the different parts of the cardiovascular system. Under aseptic precautions, following a liberal infiltration of the antecubital fossa with novcaine, an incision is made in the right or left median basilic vein. The catheter is then threaded into the vein and advanced to the desired area under fluoroscopic guidance. Spot films are taken of the various parts corresponding to the areas from which samples of blood are taken for analysis; the films are properly labelled to correspond to the blood samples. Continuous perfusion with normal saline prevents clotting of the blood in the catheter.

The comfort of the patient is important for the success of the procedure. A synthetic rubber mattress is placed on the fluoroscopic table (this does not interfere with fluoroscopy or films) and a rigid arm support is used.

ZION.

Dexter, L.: Venous Catheterization of the Heart. II. Results, Interpretations, and Value. Radiology 48:451 (May), 1947.

The use of venous catheterization in the study of congenital heart disease offers an opportunity for the estimation of the physiologic magnitudes of the shunts of blood and the circulatory dynamics.

Venous catheterization may be helpful in the recognition of atrial septal defects in the following manner: (1) The catheter may be introduced through the defect; and (2) arterial blood may be aspirated from the right auricle. The recognition of uncomplicated ventricular septal defects depends on the finding of a significantly higher oxygen content of the blood in the right ventricle than in the right auricle. A patent ductus arteriosus is detectable by finding a higher O_2 content of the blood in the pulmonary artery than in the right ventricle. The author presents several histories of confirmed cases of each of these types of congenital lesion. Charts of the O_2 content and pressure of the right auricle, right ventricle, pulmonary artery, and capillaries are included.

Since cure or improvement of certain types of congenital heart disease is possible by surgical intervention, venous catheterization promises to be an important aid in the diagnosis.

ZION.

Freeman, N. E., and Storek, A. H.: Successful Suture of the Abdominal Aorta for Arteriovenous Fistula. Surgery 21:623 (May), 1947.

The authors state that Pemberton and associates performed the first successful repair of an arteriovenous fistula involving the abdominal aorta, and that their case which is reported in this paper is the second one successfully operated upon. The patient was a battle casualty who suffered a bullet wound of the abdomen three inches below the ensiform cartilage, just to the right of the midline. He was paralyzed from the waist down. An emergency laparotomy revealed a large retroperitoneal hematoma. During the next two months, a pulsating epigastric mass with an intense thrill was noticed. Four months after injury an operative repair of the fistula was carried out through a right paramedian incision. Exposure of the aorta was obtained by incising the peritoneum and transversalis fascia to the left of the midline and reflecting the contents of the left side of the abdomen to the right. Bleeding from the aorta was controlled by passing rubber tubings around it just below the diaphragm and again just proximal to the inferior mesenteric artery. The left renal artery, also, was surrounded by tubing. The aorta was separated from the fistula and closed with a transverse running stitch of No. 000 Deknatel silk.

The postoperative course was complicated by a temporary anuria and azotemia and also by a transient increase in the paralytic signs of the lower extremities. At a follow-up examination eight months later the patient was free from recurrence of the fistula and the paralytic signs had cleared considerably.

LORD.

Rector, E. W.: Evaluation of the Basal Vascular Tone Test as an Indication for Sympathectomy in the Treatment of Surgical Lesions of the Major Arteries. *Surgery* 21:630 (May), 1947.

Naide and Säyen have described a test for the measurement of vascular tone in which the skin temperature response of the finger tips during a cooling period of fifteen minutes in a constant room temperature of 20° C. is determined. If the temperature of the finger tips is below 25° C., then the patient is considered to have high vascular tone. On the other hand if the temperature of the finger tips remains above 25° C., then the patient has low vascular tone.

By means of this test, Rector attempted to evaluate the collateral circulation of patients with a major arterial lesion of an extremity in which surgical correction of the lesion was contemplated. If the vascular tone was high, sympathectomy was employed as an adjunct measure. The results were compared with the clinical evaluation of the patient's collateral circulation and increased vascular tone, as judged by such signs as cyanosis, sweating, and constricted veins. The author concluded that the clinical evaluation of the basal vascular tone of the patients studied was more accurate than the cooling method of Naide and Säyen.

LORD.

Massell, T. B.: The Fluorescent Wheal Test for Collateral Circulation in the Preoperative Evaluation of Patients With Aneurysms and Arteriovenous Fistulas. *Surgery* 21:636 (May), 1947.

The author has studied the collateral circulation of twenty-eight patients with arteriovenous fistulas and aneurysms by means of the Matas-Moszkowicz flushing test and the fluorescent wheal test of Neller and Schmidt. For both tests a modified Matas compressor was used. When an important collateral branch arises immediately proximal to the aneurysm, both tests may give faulty information about the collateral circulation because of compression of this vessel along with the main artery leading to the aneurysm. With this exception, both tests give useful data, although the fluorescent wheal test is somewhat more accurate, simpler, and less painful to the patient, and also gives a more accurate, reproducible end-point than the Matas-Moszkowicz test.

When the collateral circulation proved inadequate, lumbar sympathetic blocks usually produced significant improvement when the collateral circulation was tested by these two methods. If improvement was noted, lumbar sympathectomy was carried out in some patients with involvement of the popliteal artery.

LORD.

Condorelli, L.: Physiopathology of the Venous Circulation. *Atti Società Italiana Cardiologia*, page 5 (May 2), 1943.

Venous pressure has been studied by means of continuous kymographic tracings. The author considers the venous system as having a "free flow" and reflecting chiefly the resistance of the veins. This resistance is the result of venous tonus. Oscillations of venous pressure of from 5 to 20 mm. of water, lasting twenty to sixty seconds, were observed. Slower oscillations, lasting from five to ten minutes, also were seen. Numerous studies concerning the regulation of venous tonus and several functional tests were studied.

The author confirms the existence of venous hypertension in acute and adhesive pericarditis, and in tricuspid stenosis. A further cause of venous hypertension is congestive failure which, paradoxically, is accompanied by increase of venous tonus. Low venous pressure is common in old age, and seems to be associated with hypotonus of the veins. The speed of venous circula-

tion was studied by two successive injections of decholin, one in a vein of the hand, the other in one of the veins of the arm (or by similar injections in the veins of the lower limb). The difference between the two circulation times represents the velocity of the blood between the two points.

The hand-to-elbow time varies from 40 to 120 seconds; the foot-to-femoral time, from 32 to 100 seconds.

LUISADA.

Selvini, A.: New Studies on the Differential Theory of the Electrocardiogram. *Cuore e circolaz* 31:69 (May-June), 1947.

The author discusses the so-called "differential theory" of the electrocardiogram. According to this, the electrocardiogram results from the algebraic summation of two monophasic curves. In order to verify this theory, the author ran a series of animal experiments. His aim was to obtain two monophasic currents, actually caused by the heart, and to determine the result of their summation.

A first series of experiments was made with two isolated frog hearts. In each of these the currents were obtained by applying an electrode over a previously injured area of the myocardium so that each of the two hearts gave a monophasic curve. When the two hearts were connected with the two electrodes of a galvanometer, the resultant curve was that of a normal electrocardiogram. A slight asynchronism between the rates of the hearts caused first simultaneous monophasic waves of an opposite direction, then progressive summation with a normal electrocardiogram.

A second series of experiments was performed on guinea pig and dog hearts. Two unipolar leads with opposite polarity from two damaged areas (one at the base, one at the apex) of the exposed heart were connected to a galvanometer through an interposed free electrical field, represented by physiologic salt solution in a Petri dish. While the two separate unipolar leads gave monophasic waves, the summation of the two, owing to a slight asynchronism, gave a nearly normal electrocardiographic complex. Various considerations on the possible applications of this differential theory follow.

LUISADA.

Macht, D. I.: Thromboplastic Properties of Penicillin and Streptomycin. *Arch. internat. de pharmacodyn. et de therap.* 74:399 (June), 1947.

An extensive investigation was undertaken by the author to ascertain the frequency and degree of the thromboplastic effects of penicillin in the blood of higher animals. Not only was the ordinary amorphous penicillin examined, but also the more recent crystalline sodium salts of penicillin and the isolated crystalline penicillin principles. Streptomycin was also tested.

In this report over 200 experiments on blood coagulation were performed by the Lee-White method. These studies were confined to the clotting of whole blood. The majority of the experiments were made on rabbits and cats, although a few experiments were also made with dog's blood and human blood.

Amorphous penicillin of every brand examined produced marked acceleration of clotting time, whether injected intravenously or intramuscularly and even when mixed with amphojel and administered by stomach tube. The onset of this property can be noted usually within fifteen or twenty minutes after injection, but in some cases it is most marked about one hour after injection. The effect persists usually for several hours. When the newly produced sodium salt of crystalline penicillin (C.S.C.) was examined, however, the thromboplastic effect was much less striking. The author secured and examined the comparative effects on coagulation of the four crystalline penicillin principles. Penicillin G (benzyl-penicillin) and penicillin F (Pentenyl-penicillin) were much less thromboplastic in their efficiency than penicillin X (hydroxy-benzyl-penicillin) and K (heptyl-penicillin). To express this in another way, penicillin X is the most thromboplastic and is followed closely by penicillin K, while penicillin G and F are not very markedly active in this respect. It was found that a small dose of penicillin X added to penicillin G produced a synergistic effect and hastened coagulation much more than a large dose of

penicillin G alone. Streptomycin was found to be also markedly thromboplastic for blood of rabbits and cats.

The author states that amorphous penicillin produces marked acceleration in clotting time, irrespective of whether it is administered by vein or parenterally. The newer crystalline penicillin (C.S.C.) was not as thromboplastic as the amorphous preparation. He points out that when rabbits were repeatedly used for these experiments, the coagulation time of those animals was shortened for long periods of time so that for examination of new preparations fresh animals had to be employed. Also, this shortening of coagulation time in rabbits and cats could be antagonized and cancelled by suitable doses of dicoumarol administered by stomach. It is the opinion of the author that, next to the chemotherapeutic properties of penicillin and streptomycin and to their low toxicity, the most important pharmacologic finding is their thromboplastic activity.

BELLET.

Vineberg, A. M., and Jewett, B. L.: Development of an Anastomosis Between the Coronary Vessels and a Transplanted Internal Mammary Artery. *Canad. M. A. J.* 56:609 (June), 1947.

In 1946, one of the authors described an anastomosis between the left internal mammary artery and the left coronary circulation, which occurred in a dog ninety-nine days after transplantation of the left internal mammary artery into the wall of the left ventricle. These experiments have been continued with the basic objective of supplying a fresh source of arterial blood to the heart muscle. To do this the left internal mammary artery has been partially removed from its normal position on the chest wall and implanted into the myocardium of the left ventricle.

In a series of dogs, the internal mammary artery was tied at its distal end between two ligatures and cut. The free end was drawn through a previously prepared tunnel in the wall of the left ventricle and fixed in this position. Ten animals were killed at the end of three or four months; seventeen animals are still alive, many of which were operated upon more than a year ago.

Of the ten dogs killed, two, or 20 per cent, showed a definite communication between the left internal mammary artery and the left coronary circulation. In eight of the ten animals which were sacrificed, the transplanted internal mammary artery had revascularized the surrounding structures. In the five animals in which a constricting scar formed, the artery proximal to this area developed communications with the chest wall and intercostal vessels on the left side. In one animal, where the artery had pulled out of the heart, a communication developed between the artery and the vessels of the chest wall and the pericardium.

BELLET.

Friedman, S. M., and Friedman, C. L.: Non-Renal Hypertension. *Canad. M. A. J.* 56:655 (June), 1947.

The authors were particularly concerned with cases of hypertension that are without any apparent renal basis in the early stages. It seemed to them that once the concept of nonrenal essential hypertension was acceptable, the rise in blood pressure might be regarded as a compensatory phenomenon. They believe that a state of equilibrium exists between the net perfusion pressure of the blood and the perfusibility of the tissues, and that an upset in this equilibrium might well demand an increase in hydrostatic pressure. Many factors are operative in the maintenance of this equilibrium. These authors were especially interested in those substances which contribute to the tissue osmotic pressure.

The testis and the vitreous humor of the eye are the major sources from which hyaluronidase has been extracted. The substrate hyaluronic acid appears to be widely distributed throughout the tissues of the body and has been related to the tissue-binding substance. The authors viewed this particular enzyme system as only one of many possible systems of that type and not necessarily the metabolic mechanism for which they were looking. The first experiment devised by the authors attempted to remove surgically the sources of hyaluronidase (mucinase) as far as possible.

Ninety male albino rats were divided into four groups: Group 1 served as untreated controls; Group 2 served as castrate controls; in Group 3, enucleation of the eye was performed at the start of the experiment; and Group 4 was composed of both castrated and eye-enucleated animals. All operations were performed on the same day. Four weeks after operation, blood pressure, renal clearance of inulin and sodium paramino hippurate (PAH), and pulse rates were determined. These tests were completed in ten days and the animals sacrificed on the fortieth day.

Renal clearance studies were carried out on ten animals from each group. The eye-enucleate animals of Group 3 failed to gain weight as well as the controls. The average blood pressure in Groups 3 and 4 was significantly elevated when compared with the controls. The weight of the testes in the animals of Group 3 was considerably below the normal, animals in this group being partially castrated by the enucleation. Moderate enlargement of the heart occurred not only in the hypertensive Groups 3 and 4, but also in the castrate controls (Group 2). Since the blood pressure was not elevated in the castrate control series (Group 2), the cardiac enlargement could not have been due to a hypertension. The clearance of both inulin and PAH was significantly elevated, both to the same degree, so that the filtration factor remained the same. There is thus a hemodynamic alteration expressed as an increase in renal blood flow. The tubular mass is likewise increased, suggesting that the kidneys are hyperfunctional.

Enucleation thus elevated the blood pressure and secondarily induced a hemodynamic and functional alteration in the kidney. A hypertension, therefore, has been produced which is neither renal nor neurogenic in origin, making it clear that the blood pressure may be raised without existing renal damage.

BELLET.

DeTakats, G., and Fowler, E. F.: The Surgical Treatment of Hypertension, the "Neurogenic" Versus Renal Hypertension From the Standpoint of Operability. Surgery 21:773 (June), 1947.

The authors point out that cases of so-called "neurogenic," that is, nonrenal hypertension traditionally have been considered suitable for sympathectomy whereas cases of hypertension due to a renal humoral mechanism have been deemed poor candidates for surgical intervention. DeTakats and Fowler challenge this concept and present detailed case reports of nineteen patients, some of whom have shown significant postoperative improvement when definite renal involvement was present but renal function reasonably good. Unilateral renal disease, renal trauma, toxemia of pregnancy, pyelonephritis, scarlatinal nephritis, and "rheumatic kidney" were the etiological bases of the renal factor in twenty-three patients with hypertension. When the functional impairment was not great, the postsympathectomy results were gratifying. On the other hand, the authors believe that neurogenic hypertension may be "a pluriglandular type of hypertension governed by the pituitary." They observed that this group fails to benefit by operative intervention on the sympathetic nervous system.

LORD.

Kebrer, H. E.: Electrocardiographic Changes Following Air Encephalograms. Deutsche med. Wchnschr. (June 6), 1947.

The author found profound changes in electrocardiograms of fifty-one patients during and following the introduction of air into the brain ventricles. There was a marked flattening of the T wave, which in some instances became negative. In addition, there was a shift of the pacemaker from the sinus node to lower auricular levels, the production of nodal rhythm, and even ventricular automatism with widening of the ventricular complexes.

The author advises that air encephalograms be undertaken with due caution in those persons whose conduction system appears to be already considerably damaged. He also concludes that low or diphasic T waves, abnormalities in the form and position of the P wave, and occasional extrasystoles at times have an extracardiac origin. The author mentions briefly the results obtained by various workers which might suggest that the midbrain is one of the extracardiac sources of origin of these ectopic rhythms.

KRAMER.

Cavelti, P. A.: *Studies on the Pathogenesis of Rheumatic Fever. II: Cardiac Lesions Produced in Rats by Means of Autoantibodies.* Arch. Path. 44:13 (July), 1947.

Killed streptococci in conjunction with emulsions of heart, connective tissue, and skeletal muscle can cause the development of antibodies to homologous tissues. Can these antibodies react specifically, in vivo, with respective tissue components and act as a pathologic agent? The hearts of rats thus immunized were studied from the standpoint of myocardial and valvular disease and its possible resemblance to the human lesions of rheumatic fever. Grossly, little was noted, since the smallness of the rat heart precluded detailed examination. Histologically, the chief changes occurred in the connective tissue structure of the heart; namely, the valves, valve rings, and the interstitial and perivascular tissue of the myocardium. The valvular lesions were at the free ends and in the valvular rings, and consisted of infiltrative cellular lesions, often nodular. Various cellular types were present: the monocytic series predominated; fibroblastic proliferation and relatively large basophilic cells contributed. Some of the latter were multinuclear; together with connective tissue degeneration and frequent nodular formation the combined features suggested Aschoff bodies, yet classical lesions of the latter type could not be identified with certainty. These infiltrations caused definite thickening of some valve leaflets. Similar lesions were found in the connective tissue of the myocardium. Widespread fibroblastic activity and subsequent scarring were also notable in the myocardium of many of the rats.

Lesions resembling periarteritis nodosa were seen around arterial vessels in the heart and also in other organs.

No similar cardiac lesions were seen in the hearts of rats treated with streptococci alone or connective tissue emulsion alone. Cavelti concluded that the lesions were due to the presence of autoantibodies. He further concluded that tissue emulsions from the heart and connective tissue were equally potent in the production of the cardiac lesions, tissue emulsions from skeletal muscle were the least so. Connective tissue is apparently the site of the antigen responsible for the cardiac lesions.

Cavelti formulates a hypothesis of the genesis of rheumatic fever as follows: Streptococcic substances reacting with connective tissue of the host lead to formation of autogenous antigen. This antigen incites the development of specific antibodies, which in turn precipitate the rheumatic lesions by reacting, in vivo, with the antigen situated in the tissues.

GOULEY.

Alexander, F., Gold, H., Katz, L. N., Levy, R. L., Scott, R., and White, P. D.: *The Relative Value of Synthetic Quinidine, Dihydroquinidine, Commercial Quinidine, and Quinine in the Control of Cardiac Arrhythmias.* J. Pharmacol. & Exper. Therap. 90:191 (July), 1947.

Using a large group of subjects with paroxysmal auricular fibrillation, auricular flutter, ventricular tachycardia, and auricular fibrillation, the authors were able to show that the action of synthetic and commercial quinidine, given in the same dosage, was similar in both degree of slowing and duration of effect. Both were equally effective in the prophylaxis of cardiac arrhythmias. Dihydroquinidine, used in half the dosage of synthetic and commercial quinidine, had a similar action. Quinine compared to synthetic and commercial quinidine and dihydroquinidine was relatively ineffective.

GODFREY.

Wilburne, M., Katz, L. N., Rodburd, S., and Surtshin, A.: *The Action of N, N-Dibenzyl-Beta-Chloroethylamine (Dibenamine) in Hypertensive Dogs.* J. Pharmacol. & Exper. Therap. 90:215 (July), 1947.

The authors studied the effect of intravenous injection of dibenamine in seven hypertensive (renal hypertension) dogs. Three normotensive dogs were used as controls. The animals were unanesthetized, and the pulse rate and blood pressure readings were followed over periods of from two days to several weeks.

Both the hypertensive and normotensive dogs showed the same type of reaction to intravenous dibenamine. An initial fall in blood pressure and rise in pulse rate was followed by a widely fluctuating blood pressure which persisted for as long as two days after a single dose. Prolonged administration of dibenamine over a period of three weeks produced no sustained effect upon the blood pressure of three hypertensive dogs. Dibenamine shortened or inhibited adrenalin-produced ventricular tachycardia and reduced the pressor response to adrenalin.

GODFREY.

Chen, K. K., and Anderson, R. C.: Digitalis-Like Action of Some New Glycosides and Esters of Strophanthidin. *J. Pharmacol. & Exper. Therap.* 90:271 (July), 1947.

Ten new glycosides related to digitalis-like glycosides and five esters of strophanthidin were tested. The mean lethal dose was determined. In some, the action compared favorably with that of ouabain.

GODFREY.

Crystal, D. K., Edmonds, H. W., and Betzold, P. F.: Symmetrical Double Aortic Arch. *West. J. Surg.* 55:389 (July), 1947.

The authors present in an 8-week-old infant a case of double, symmetrical right and left aortic arches, which embraced the trachea and esophagus tightly and which united dorsal to the esophagus to form the descending aorta.

At the age of 10 months, generalized convulsions followed some of the apneic attacks to which the child was subject. It was observed that the superficial veins of the torso and neck had become a great deal more prominent. A barium study of the esophagus showed a constant indentation of the esophagus from behind at the level of the second and third dorsal vertebrae. This was interpreted as the aortic arch passing behind the esophagus. The symptoms could then be explained on the following assumptions: (a) a persistent right aortic arch; (b) the descending aorta lying in its normal position to the left of the vertebral column; and (c) constriction of the esophagus and trachea by a left aortic arch, or by the ligamentum arteriosum, or by both the arch and the ligament.

When the patient was one year old, operation was attempted. The atresic ductus arteriosus was ligated and cut. At the time of operation, it was considered unwise to incise the pericardium any further cephalad because of its intimate connection with the trachea. Two hours post-operatively, the patient developed an attack similar to those experienced before operation, became apneic, and died.

Autopsy disclosed symmetrically placed right and left aortic arches of equal caliber tightly embracing the trachea and esophagus. From each of these arose the carotid and subclavian arteries to the respective sides. Behind the esophagus, the arches merged to form a descending aorta which extended downward in its normal position. The pericardium was attached above to the two arches. The left arch lay in the fold of pericardium which had seemed adherent to the trachea.

BELLET.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: The Circulatory Action of Theophylline Ethylene Diamine. *Clin. Sc.* 6:125 (July 17), 1947.

The authors have made studies of right auricular pressure by means of cardiac catheterization, and of the cardiac output determined by the Fick principle in a group of normal subjects as well as patients with various forms of heart failure. The effect of theophylline ethylenediamine, 0.48 Gm. administered intravenously, on these observations was noted. Except in cases of emphysema, the administration of this drug was followed by a fall in venous pressure and a corresponding rise in cardiac output. This rise in cardiac output was greater than that which occurs when venous pressure falls following the application of cuffs, or after venesection, or the administration of digoxin, and led the authors to agree with others that this drug exerts an adrenaline-like action upon the myocardium.

WAGNER.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: **Effects of Oxygen, Venesection and Digitalis in Chronic Heart Failure From Disease of the Lungs.** Clin. Sc. 6:187 (July 17), 1947.

This paper reports observation on cardiac output and filling pressure in cases of congestive heart failure associated with emphysema and other chronic diseases of the lungs. These patients were divided into two groups: Patients in the first group had systolic blood pressures over 90 mm. Hg and had an increased cardiac output. Patients in the second group had systolic blood pressure below 90 mm. Hg; they were in a terminal state and exhibited a low cardiac output. Patients in the first group differed from patients with congestive heart failure due to hypertensive, ischemic, or valvular heart disease because they presented an increased cardiac output, and they further differed in that they showed a fall in cardiac output when a fall in venous pressure occurred. The authors state that the increased cardiac output found in this condition is compensatory, and harm may follow a fall in venous pressure produced by venesection or digoxin. The measures of greatest value are oxygen and thiouracil. The latter is given in an effort to reduce the general metabolism.

WAGNER.

Garvin, E. J.: **Mesenteric Vascular Occlusion Complicating Thromboangiitis Obliterans.** Am. J. Surg. 74:211 (Aug.), 1947.

The author reviews the brief literature on Buerger's disease in which vascular involvement of the abdominal vessels has been established. The diagnosis is based on four chief findings: (1) The clinical picture is not typical of the common surgical emergencies; (2) the degree of pain is out of proportion to the other clinical findings; (3) the only constant finding is deep abdominal tenderness unless peritonitis has developed, which is a late manifestation; and (4) the leucocyte count and pulse rate are elevated disproportionately to the temperature and other signs.

Garvin reports a case of a man, 33 years of age, who had suffered from Buerger's disease of the extremities for eight months, and who developed an acute occlusion of a large branch of the mesenteric vein. Operative resection of one and one-half feet of gangrenous bowel located in the proximal ileum was carried out. The patient was treated postoperatively by gastric decompression, penicillin, and parenteral fluids. In addition, he was heparinized for seven days. The postoperative course was moderately febrile, but recovery was complete by the twenty-fifth postoperative day, when he was discharged.

The author concludes that "in spite of the fact that the vessels in the resected portion of bowel did not show microscopically the ordinary vascular lesions seen in the thromboangiitis obliterans, yet in view of the present literature on this subject, we must consider the mesenteric vascular occlusion as part of the general picture of Buerger's disease."

LORD.

Cavelti, P. A.: **Pathogenesis of Glomerulonephritis and Rheumatic Fever.** Arch. Path. 44:119 (Aug.), 1947.

In previous work, the author demonstrated the formation of autoantibodies to kidney, heart, and connective tissue by immunizing rats and rabbits with emulsions of homologous tissues combined with killed streptococci. He showed, further, that such autoantibodies are pathogenic when they react with the corresponding tissues in situ. Such a process might explain the pathogenesis of rheumatic fever and glomerulonephritis. The author previously obtained streptococcus-tissue antigen corresponding to the hypothetical autoantigens by mixing (in vitro) the killed streptococci with tissue emulsions.

He now demonstrates that, with focal streptococcic lesions in rats, autogenous tissue antigens are developed and released into the blood stream. Their presence can be proven by means of antisera to rat tissues produced in the rabbit. The most potent rabbit anti-rat tissue serum was anti-kidney serum, which reacted with the sera of the infected rat in high dilutions; this striking positive reaction was obtainable in maximum degree in twenty-four or thirty-six hours

after the initiation of streptococcic infection, and disappeared gradually in from eight to fourteen days. Rabbit anti-rat heart serum produced a much weaker reaction.

Although this phenomenon is similar to rheumatic fever in so far as the latter may be the expression of the formation of autoantibodies in response to streptococcic infection, there is one dissimilar feature: this experimental reaction appears quickly at the height of streptococcic infection, while rheumatic fever appears two or three weeks after the onset of the preceding streptococcic infection.

GOULEY.

Pearce, J. M., and Lange, G.: Cardiac Anoxia as the Factor Determining the Occurrence of Experimental Viral Carditis. Arch. Path. 44:103 (Aug.), 1947.

The authors reviewed previous work dealing with the production of a viral myocarditis in rabbits secondary to subcutaneous inoculations or installations in the upper respiratory tract. They found that such myocardial lesions were remarkably increased by the simultaneous intravenous injection of acacia and also of pitressin extract. The authors feel that the only reasonable explanation for this phenomenon is the introduction of the factor of cardiac anoxia. This is produced by coronary artery constriction after pitressin, or by interference with gas interchange between hemoglobin and the tissues of the heart following acacia. If the authors' hypothesis is correct, the use of other drugs that would cause coronary constriction should cause the same aggravation of viral myocarditis as did pitressin. On the other hand, those drugs that have a detrimental action on heart muscle, without coronary constriction, should have no effect in increasing the extent of viral myocarditis.

In conformity with this reasoning, barium chloride and adrenalin were tried and found to cause a marked increase in the incidence of viral myocarditis. On the other hand, digitalis, papaverine, and nikethamide, given intravenously, produced no increase of inflammatory reaction in the hearts of untreated controls.

The myocardial lesions that developed after acacia had been injected into the venous blood stream were predominantly confined to the right side of the heart, while those following the injection of constrictors of the coronary arteries involved chiefly the left ventricle. This can be explained by the almost complete dependence of the left ventricular myocardium on the coronary arteries for its nutrition, while the right ventricular muscle is nourished by the numerous venous and venosinuosidal communications that link with the right ventricle lumen.

GOULEY.

Winbury, M. M., and Crittenden, P. J.: The Action of the Basic Amino Acids on the Heart and Intestine. J. Pharmacol. & Exper. Therap. 90:293 (Aug.) 1947.

The authors studied the action of the basic amino acids (histidine, arginine, and lysine) on the heart and intestine, using both isolated and intact specimens. Arginine and lysine were found to depress the isolated frog heart, while histidine exerted a stimulating action.

Using the intact anesthetized cat, arginine and lysine, given intravenously in a solution buffered to pH 7.4, had a hypotensive action with a decrease in heart rate. Histidine at the same pH resulted in a slight rise in blood pressure. However, if given as a monohydrochloride at pH 4.0, histidine exhibited a hypotensive action similar to arginine and lysine.

Studies on the intestine of the rabbit *in situ* revealed a fundamental difference between the action of histidine hydrochloride and the two basic amino acids. All three relaxed the longitudinal muscles of the duodenum. However, histidine hydrochloride caused a spasm of the circular muscles, while lysine and arginine caused an inhibition.

GODFREY.

Maresh, G. J., and Farah, A. E.: The Influence of Rate of Administration Upon the Lethal Dose of Cardiac Glycosides. J. Pharmacol. & Exper. Therap. 90:304 (Aug.), 1947.

Digoxin, oleandrin, and digitoxin were given intravenously to intact anesthetized cats. The more rapidly the individual glycoside was given, the higher was the lethal dose. As the rate of

administration was decreased, the lethal dose was diminished until a definite concentration was reached which could not be lowered by further decrease in rate of administration. This is termed the minimal lethal dose. Each glycoside has a characteristic rate of administration at which the minimal lethal dose is determined.

GODFREY.

Rogers, J. W., Sellers, E. A., and Gornall, A. G.: **Intestinal Perfusion in the Treatment of Uremia.** *Science* 106:108 (Aug.), 1947.

Interest in removal of nonprotein nitrogenous constituents of blood by "artificial" means in cases of renal failure has been stimulated greatly by recent work. Kolff suggested that perfusion of a loop of bowel isolated surgically might prove superior in some respects to other methods presently used. It occurred to one of the authors (J.W.R.) that a specially designed intestinal tube with three lumina might make it possible to perfuse the intestine in situ, and so render surgical intervention or even aseptic technique unnecessary. By using a thin triple bore tube with a small balloon at the tip, the authors were able experimentally to perfuse any desired length of intestine without resorting to surgery on the bowel. In the dog, however, it is necessary to manipulate the tube into position through an abdominal incision. This would be unnecessary in the human.

In experiments to date, the blood nonprotein nitrogen of nephrectomized dogs has been reduced consistently and materially. For example, a lowering of the azotemia from 198 to 126, 198 to 112, and 231 to 145 mg. per 100 ml. of blood was observed in successive trials, using 12 to 18 liters of perfusion fluid over a period of about six hours. The rinsing fluid after perfusion contained 4.3 to 5.4 Gm. of nonprotein nitrogen.

A more detailed experimental study of the method is now in progress and an investigation of its clinical application is being undertaken by the authors.

BELLET.

Foisie, P. S.: **Traumatic Arterial Vasospasm.** *New England J. Med.* 237:295 (Aug. 28), 1947.

The author discusses the findings observed in a group of patients suffering from the persistence of a relatively low-grade arterial spasm in the extremities as a complication of local injury. He points out that this type of response holds little or no threat to the viability of the limb, but, nevertheless, it is likely to cause nutritional changes which may adversely affect the functional result. No relationship exists between the severity of the original wound and the degree of arterial spasm subsequently noted. In fact, some of the most stubborn cases of vasospasm may complicate mild injuries. It would appear that the smaller, quickly closed wounds are associated with more vasospasm than are the larger, wide open ones. The production of tension in the tissues may, therefore, be a factor in the initiation and propagation of this reaction. The incidence of vasospasm is not dependent on the location of the injury nor on the structures involved.

The clinical picture of the existence of vasospasm consists primarily of color changes, involving a combination of spotty pallor and diffuse cyanosis. Dependency and exposure to a cold environment increase the cyanosis, while elevation of the extremity has a similar effect on the pallor. The cutaneous temperature of the affected limb is definitely lower than that of the normal side, and generally there is a moderate edema. The severe excruciating pain generally noted in causalgia is absent, but the patient complains of numbness, coldness, tingling, or other types of paresthesia. There is marked tenderness, out of proportion to the force of palpation, and the extremity is held immobile with the joints flexed in an attempt to minimize the pain. The most reliable sign of arterial spasm is the finding of diminished or absent peripheral pulses which are definitely altered by vasodilating procedures.

With regard to therapy, it appears necessary to maintain the extremity in a fairly warm environment and to utilize the various vasodilating procedures. Of the latter, repeated paravertebral sympathetic blocks cause transient but definite improvement. Sympathetic gangliectomy will in some instances produce permanent relief of symptoms.

ABRAMSON.

Starr, I.: On the Later Development of Heart Disease in Apparently Healthy Persons With Abnormal Ballistocardiograms. Eight- to Ten-Year After-Histories of 90 Persons Over 40 Years of Age. Am. J. M. Sc. 214:233 (Sept.), 1947.

Ballistocardiograms were first taken in 1936. When the method was satisfactorily established, work on normal standards was begun. Normal subjects were selected from a group that would permit a follow-up over a period of years. Ten years have elapsed since the first record of this series was taken, eight years since the last. Among the ninety supposedly healthy persons in this group, ranging from 40 years to 85 years of age, four subjects had ballistocardiograms abnormal in form. Three of the four developed coronary heart disease in the years which followed. In the other eighty-six subjects the ballistocardiograms were normal in form. In these the results were arranged according to the size of the ballistocardiogram as related to actual and ideal weight. The six cases giving the smallest records in proportion to actual weight developed coronary heart disease. It was found that a line could be drawn through the data at a level 44 per cent below the average of healthy young adults referred to ideal weight, and that 50 per cent of those who fell below this line developed serious heart disease in contrast to 5 per cent of those above, a highly significant difference. Five subjects who gave ballistocardiograms normal in form and amplitude during the years 1937-39 died within the next eight to ten years. None of them developed clinical evidence of heart disease, and in two the heart was normal at necropsy. Post-mortem examinations were not done in the other three. One patient in the group with normal ballistocardiograms is of especial interest. This man, aged 79 years when originally studied, had a record which was above those of most others in his age group and equal to that of many young adults. This man is now well and active at the age of 87 years.

It is concluded from these studies that a ballistocardiogram which is abnormal in form or of unusually small amplitude is of serious prognostic significance. The ballistocardiographic method gives promise of identifying coronary heart disease far earlier in its course than has been possible hitherto.

DURANT.

White, P. D. August, S., and Michie, C. R.: Hydrothorax in Congestive Heart Failure. Am. J. M. Sc. 214:243 (Sept.), 1947.

The authors have analyzed 100 cases of congestive heart failure showing hydrothorax at autopsy at the Massachusetts General Hospital. Fifteen cases showed unilateral right hydrothorax; thirteen, unilateral left hydrothorax. Each of the latter revealed an important factor in addition to the congestive failure, there being complete obliteration of the right pleural cavity in twelve and unilateral left pulmonary infarction in the remaining case, in contrast to only four such explanations among the fifteen cases of unilateral right hydrothorax. The remaining seventy-two cases showed bilateral pleural effusions, equal in thirty-one but predominantly right-sided in thirty-two of the remaining forty-one. The etiological type of heart disease and the side of preponderant initial ventricular strain made little difference as to the location of the hydrothorax, but the great majority of these cases at autopsy had right heart failure usually superimposed on left.

An additional 100 cases of acute left ventricular failure in hypertension or aortic valve disease were analyzed as to the subsequent occurrence of hydrothorax during the next few weeks; seventy-six showed none, while sixteen developed bilateral hydrothorax, six unilateral right, and only two unilateral left hydrothorax; of the twenty-four cases who developed hydrothorax, only six failed to show any recognized sign of right heart failure and it is possible that the venous pressure might, if recorded, have been elevated in those six cases also. Pulmonary infarction (superimposed upon, or precipitating, or aggravating the congestive failure) was found in thirty cases and played a secondary role in the localization of the hydrothorax.

DURANT.

Mussee, J. C.: Atrial Septal Defect. Correlation of Autopsy Findings With Data Obtained by Right Heart Catheterization. Am. J. M. Sc. 214:248 (Sept.), 1947.

Of 1,500 patients studied by the method of heart catheterization, only one patient with atrial septal defect has come to autopsy. The literature has revealed no other case report of congenital

cardiac defect which had both heart catheter studies and autopsy. The case reported was that of a man 37 years of age, who had been diagnosed clinically as having congenital heart disease with myocardial failure and compensatory polycythemia. The right heart catheterizations revealed that: (1) the oxygen content of the right atrial blood was distinctly higher than the superior vena caval blood; (2) the oxygen content of the right atrial and right ventricular blood was the same; (3) the right ventricular (pulmonary artery) pressure was extremely high (140 mm. Hg); (4) the pressure in the right atrium was elevated; (5) calculated left ventricular output was roughly normal, right ventricular output was at least twice this. These data could only have been obtained by heart catheterization, and they helped to clarify the diagnosis of atrial septal defect and made possible the diagnosis of pulmonary vascular hypertension. After these studies, the course of the patient's condition was gradually downhill over a period of eight months. Death occurred after a series of pulmonary infarcts.

The autopsy showed a defect in the lower portion of the interatrial septum which was 5 cm. in diameter. There was marked dilatation and hypertrophy of the heart, predominantly right-sided. Bilaterally, thrombosis of many branches of the pulmonary artery, with multiple pulmonary infarcts, was found.

In discussing the correlation of the autopsy findings with the catheterization studies, it is pointed out that right atrial blood oxygen saturation can exceed the vena caval saturation in only two conditions: interatrial septal defect and aberrant pulmonary veins emptying into the right atrium, the latter condition being rarer than the former and not associated with as much cardiac enlargement. The finding of a right ventricular output roughly twice that of the left ventricle, despite the fact that the right atrial pressure was necessarily less than the left, is at variance with Starling's law. The discovery of increased right ventricular pressure, together with the fact that increased saturation of arterial blood could be obtained with oxygen inhalation, showed the presence of pulmonary vascular obstruction.

DURANT.

Fitts, W. T., Jr., and Wells, E. J., Jr.: A Case of Fatal Arterial Occlusions Due to Aneurysm of the Abdominal Aorta. Am. J. M. Sc. 214:252 (Sept.), 1947.

A rare complication of aortic abdominal aneurysm is reported. A 66-year-old tabetic was admitted to the hospital for scrotal gangrene, developed signs of an abdominal catastrophe, and died a few hours after admission. Autopsy showed a saccular aneurysm of the lower abdominal aorta. A thrombus in the inferior mesenteric artery had produced gangrene of the large bowel, while embolic occlusions of the hypogastric arteries were evidently responsible for the scrotal and perineal gangrene. A search of the literature failed to reveal a similar case.

DURANT.

Shapiro, E., Lipkis, M. L., and Kahn, J.: "Trophic" Ulcers of the Hands Complicating Myocardial Infarction. Am. J. M. Sc. 214:288 (Sept.), 1947.

Certain maladies of the shoulder joint, subdeltoid bursa, palmar fascia, and finger joints are recognized as sequelae of myocardial infarction. "Trophic" ulceration of the hands, however, is a rare and apparently hitherto unreported complication. The patient, a man aged 49 years, had had angina since the age of 41 years. About twelve hours after the onset of the symptoms of acute posterior myocardial infarction, two vesicles, symmetrically placed over the metacarpophalangeal joints of the index fingers, were noted. The thin coverings of these blisters ruptured spontaneously the next day and deeply punched out, painless ulcers were left, the right being twice as large as the left. There were no neurologic signs, no thickening of the palmar fascia, no arthritis of the hands, and no evidence of bursitis of the "shoulder syndrome." The pain of the myocardial infarction and of the preceding angina had been entirely limited to the chest, there being no arm radiation whatsoever. The authors believe that the promptly appearing vesicular and, later, ulcerated skin lesions in this case may be explained by antidromic stimulation of prodigious degree from the infarcted heart, and they suggest that antidromic impulses may be the mechanism of production of the other maladies of the shoulder and hand following myocardial infarction.

DURANT.

Geever, E. F.: Pulmonary Vascular Lesions in Silicosis and Related Pathologic Changes.
Am. J. M. Sc. 214:292 (Sept.), 1947.

The effect of silicosis on the pulmonary circulatory system and, indirectly, on the right heart constitutes one of the important complications of this disease. Such sequelae as pulmonary hypertension and right-sided cardiac dilatation, hypertrophy, and failure are generally attributed to obliterative vascular changes. However, with one exception, detailed descriptions of the vascular lesions and their pathogenesis are not available in the modern literature.

The author has studied the pulmonary vascular lesions and related pathologic changes in forty-three cases of silicosis, cases with complicating pulmonary tuberculosis being largely excluded. A similar series of forty-three nonsilicotic patients in the same age group was used as a control. Two morphologic processes seemed to evoke vascular changes: direct encroachment on the vascular wall by nodules or nodular masses, and infiltration of the vascular wall by dust and pigment-bearing granulation tissue. In discrete nodular silicosis the vascular lesions were not striking, as a rule, and were found only in small arteries, small veins, arterioles, venules, and capillaries. In massive conglomerate nodular silicosis the vascular lesions were severe, were found in vessels of all sizes, and were demonstrable best in sections stained for elastic fibers. Fibroblastic proliferation was an early reaction in all layers of the arterial wall; later, proliferation of vasal and capillary channels and degeneration of muscle and elastic tissue occurred. Occlusion and disruption of the vascular wall by infiltrating granulation tissue which streamed through all the layers were end results. Thrombosis of large arteries was observed in two cases of discrete nodular and seven cases of massive conglomerate nodular silicosis. The veins revealed similar occlusive and disruptive changes, but appeared to offer less resistance than the arteries. Lymphatic vessels often showed distention, stasis, and endothelial pigmentation. In massive conglomerate nodular silicosis, veins and lymphatics were often destroyed without trace.

Related pathologic changes in the heart included right ventricular hypertrophy to a thickness of 0.5 cm. or more in ten out of the twenty cases in the discrete nodular group, and in sixteen out of twenty-three cases in the massive conglomerate nodular group. Although seven patients in the former group had evidence of cardiac disability which was of major importance as a cause of death, only one instance was found in which the right-sided cardiac changes alone were responsible. Thirteen of twenty-three patients in the latter group had evidence of a major cardiac disability. In ten hearts of this group, right ventricular hypertrophy and varying degrees of dilatation were the only significant changes. Related pathologic changes in the pulmonary parenchyma (namely, fibrosis, ischemic necrosis, and ischemic cavitation) were described. Ischemic cavitation was found in the fibrous masses of seven patients in the conglomerate nodular group. Pseudocavitation due to emphysema was sometimes encountered.

Intravascular pressure changes were believed to be important factors in the pathogenesis of the vascular lesions in these silicotic patients. Increased pulmonary intra-arterial pressure due to elimination of large portions of the pulmonary vascular bed plus interference with distensibility of the remaining channels, surrounded or fixed as they are at various points by fibrous masses, would be expected to be combined deleterious factors in this respect. Anoxemia due to interference with vasal circulation was believed to result from the marked perivascular fibrous changes in massive conglomerate nodular silicosis. Adventitial vasal hyperemia and proliferation probably represented a reaction to interference with vasal circulation and an attempt to establish collateral channels.

DURANT.

Wilens, S. L.: Resorption of Arterial Atheromatous Deposits in Wasting Disease.
Am. J. Path. 23:793 (Sept.), 1947.

At necropsy, severe atheromatosis is at least twice as common in obese as in undernourished persons who are 35 years of age or older. This relationship is independent of sex, hypertension, and diabetes. The author believes that atheromatosis in man, as well as in rabbits, may be reversible, and bases this opinion on studies of autopsy material with special reference to the appearance of the aorta and coronary arteries of patients whose nutrition was known to have been

seriously impaired during their final illness. He correlated data as to the state of nutrition during health, the duration of the final illness, and the loss of weight during that time. Only patients between 40 and 60 years were included.

The evaluation of the state of nutrition at autopsy was based on the amount of adipose tissue deposited in the various body sites. The degree of atherosclerosis was graded by the extent of atheromatous deposit in the intima. The relationship of terminal weight loss and nutrition and the severity of atherosclerosis in the coronary arteries and in the aorta was striking. Twelve of twenty-four obese patients, but only two of thirty-nine poorly nourished patients, had severe atherosclerosis of the coronary arteries. If hypertensive patients are excluded, this difference is still apparent. Of the twelve obese patients, six were hypertensive, while both of the poorly nourished patients with severe atherosclerosis were hypertensive. The aorta is apparently as good a site as the coronary arteries by which to judge the relationship of nutrition and atheromatosis.

GOULEY.

Jorpes, J. E.: The Origin and the Physiology of Heparin; the Specific Therapy in Thrombosis. *Ann. Int. Med.* 27:361 (Sept.), 1947.

The composition of heparin is essentially that of a sulfonic ester of a high molecular polysaccharide. Its anticoagulant action is apparently related to the strong negative electric charge of the compound. The neutralization of the anticoagulant property of heparin is effected by protamine presumably because of the positive charge carried by protamine. A significant but unexplained finding is the stronger anticoagulant property of dog heparin, as compared with ox, pig, and sheep heparin, in spite of the fact that they all have the same content of ester sulfuric acid. In spite of its high degree of ionization in solution, heparin exerts very little osmotic pressure and, therefore, will not cause shrinkage of red blood cells either in vivo or in vitro.

The mast cells of Erlich, which are in close proximity to all capillaries in the body, constitute the site of formation of heparin. These cells supposedly extrude their contents into the peripheral tissue juices or almost directly into the blood stream. The liberation of the heparin in physiologic amounts from this hormonal system of mast cells maintains the proper equilibrium in so far as coagulation of the blood is concerned.

The results obtained with heparin by various writers, as well as by the author, in the treatment of thrombosis of the leg veins and of the pulmonary artery are analyzed. All these assembled data, which are based on a large experience over a number of years, indicate that the incidence of fatal embolism and disabling aftereffects of venous thrombosis have been dramatically reduced. The average dose recommended is 400 mg. divided over a twenty-four hour period. During such treatment, blood clotting determinations are not made except in elderly patients with impaired renal function.

Since heparin is highly active and nontoxic, its prophylactic use is recommended after operations or childbirth where there have been single or recurrent attacks of thrombosis in the history of the patient.

WENDKOS.

Allen, E. V., Hines, E. A., Jr., Kvale, W. F., and Barker, N. W.: The Use of Dicumarol as an Anticoagulant: Experience in 2,307 Cases. *Ann. Int. Med.* 27:371 (Sept.), 1947.

This paper summarizes the results obtained, over a six-year period, in (1) the treatment of venous thrombosis, arterial embolism and thrombosis, and pulmonary embolism with dicumarol or heparin combined with dicumarol in a total of 988 cases; (2) the prevention, with dicumarol, of pulmonary embolism or venous thrombosis, post partum or postoperatively, in a total of 1,238 cases; and (3) the treatment with dicumarol of myocardial infarction in a total of fifty cases.

The authors recommend that dicumarol should be used whenever an anticoagulant effect is needed over a period of days, weeks, months, or years, provided that there are available reliable determinations of the value for prothrombin in the blood. However, when both a rapid and a

prolonged effect of an anticoagulant are desired, heparin and dicumarol should be administered simultaneously. It is recommended that dicumarol be used cautiously or not at all in renal insufficiency, after operations on the brain or spinal cord, in blood dyscrasias, in ulcerative lesions of the gastrointestinal tract, and in nutritional deficiency or hepatic diseases associated with potential or actual prothrombin deficiency. The use of anticoagulants is not advised in subacute bacterial endocarditis since the danger of hemorrhage is relatively great. The dosage of dicumarol is discussed and it is concluded that the amount required will depend on the prothrombin percentage. In the author's experience, this should be maintained between 10 and 30 per cent. In the 1,983 postoperative cases, minor hemorrhage (epistaxis, hematuria, and localized ecchymosis) occurred in 3.4 per cent, while serious bleeding (from operative wounds or from the gastrointestinal tract) occurred in 1.8 per cent of the cases. Death from such serious hemorrhage occurred only twice. Serious bleeding was found to be easily controllable by repeated administration of vitamin K and transfusions of fresh blood. The post-partum state was not considered a contraindication to the use of dicumarol in the treatment of venous thrombosis or pulmonary embolism which occurred following delivery. It is the author's opinion that the introduction of dicumarol has eliminated the need for surgical ligation of veins in order to prevent pulmonary embolism.

Fatal pulmonary embolism was prevented and arterial thrombosis was halted in most instances. In addition, early treatment of sudden arterial occlusion with anticoagulants has resulted in survival of the extremity in 90 per cent of instances of embolism and 80 per cent of instances of thrombosis. An overall consideration of 1,513 postoperative patients treated with anticoagulants indicated that eighty-five patients survived who would have been expected to die from pulmonary embolism, and 250 patients were spared venous thrombosis or nonfatal pulmonary embolism. In 506 additional postoperative cases in which dicumarol was used prophylactically, venous thrombosis occurred in but two instances; there was no pulmonary embolism. The results in the fifty cases of acute myocardial infarction indicated that there was a substantial reduction in the incidence of further myocardial infarction and of arterial embolism and venous thrombosis.

WENDKOS.

Perera, G. A., and Blood, D. W.: Pressor Activity of Desoxycorticosterone Acetate in Normotensive and Hypertensive Subjects. *Ann. Int. Med.* 27:401 (Sept.), 1947.

Desoxycorticosterone acetate was administered to ten normotensive subjects and fourteen patients with uncomplicated hypertensive vascular disease in doses of 5 mg. subcutaneously twice daily for one week. No significant change of the resting blood pressure appeared in the normotensive group, whereas definite increases in systolic and diastolic readings were observed in the hypertensive patients. The prompt rise in blood pressure of patients with hypertension could not be ascribed to changes in salt or water retention alone, as there were comparable changes in the normotensive group.

WENDKOS.

David, P., McPeak, E. M., Vivas-Salas, E., and White, P. D.: Dissecting Aneurysm of the Aorta: Review of 17 Autopsied Cases of Acute Dissecting Aneurysm of the Aorta Encountered at the Massachusetts General Hospital From 1937 to 1946 Inclusive, Eight of Which Were Correctly Diagnosed Ante Mortem. *Ann. Int. Med.* 27:405 (Sept.), 1947.

During the ten years from 1937 to 1946, seventeen cases of acute dissecting aneurysm, proven by necropsy, were encountered at the Massachusetts General Hospital. Of these, twelve were men and five women. The men ranged in age from 47 to 69 years, and the women from 57 to 78 years. A correct ante-mortem diagnosis was made in eight instances. Associated hypertension existed in every case, but in two instances syphilitic heart disease was also present. A basal diastolic murmur developed during the acute dissection of the aorta in the majority of the cases, and was, therefore, considered an important diagnostic sign. Since electrocardiographic changes characteristic of acute myocardial infarction were lacking in this series, this finding is

suggested as an important means for differentiating the pain of acute coronary occlusion from that of acute dissecting aneurysm. Tears in the aortic intima, classified as initial, were located in the upper aorta in nineteen instances. Sixteen presented evidence of being recent, the other three appeared to be well healed and communicated with dissected endothelialized aneurysmal sacs. Eleven of the nineteen initial intimal tears were located within the first 3 cm. of the ascending aorta, six in the ascending aorta beyond the 3 cm. level, one in the arch, and the remaining example in the thoracic aorta. It was more difficult to identify the site of the rupture of the adventitia, through which blood escaped from the sac into the surrounding tissues or serous cavities. Rupture of the dissecting aneurysmal sac into the original lumen was discovered in six instances, in two of which the secondary tear had occurred in the abdominal portion of the aorta and in the other four in one of the iliac arteries. Considering involvement of the main branches of the aorta in the dissecting process in order of frequency, the iliac arteries were affected in eight cases, the great vessels of the arch in six, the renal arteries in six, the celiac axis in five, the mesenteric arteries in five, and the coronary arteries in three cases. An arteriosclerotic involvement of some part of the aorta was described in every case. Medionecrosis, which is now recognized as being by far the main etiological factor of dissection of the aorta, was found in thirteen cases; it was not typical in two cases and was absent in the other two cases. Nine patients died within twenty-four hours and six within one to six days following the onset of the aortic dissection. A healed dissecting aneurysm which had developed previously, was noted at necropsy in three of the cases. The immediate cause of death was acute dissection of the aorta in only two cases, whereas in the remainder, it was hemorrhage into the pericardial sac with resultant cardiac tamponade.

WENDKOS.

Mellinkoff, S. M., and Higgins, J. R.: *The Heart Rate in Malaria; a Review of 90 Cases.* Ann. Int. Med. 27:433 (Sept.), 1947.

The authors studied the heart rate during bouts of pyrexia in ninety cases of malaria, confirmed by the identification of the parasite in thin or thick blood smears. Of these, eighty-five were examples of infection with *Plasmodium vivax*, two with *Plasmodium falciparum*, and three with *Plasmodium malariae*. The results of the study indicated that one-fourth of the patients had a relative bradycardia, which, however, was never less than 70 per minute.

WENDKOS.

Solarz, S. D.: *So-called "Infarction Type" Electrocardiographic Changes Following Paroxysmal Tachycardia.* Ann. Int. Med. 27:447 (Sept.), 1947.

The author describes a case of a 40-year-old aviator whose electrocardiograms for a two-week period following cessation of an attack of paroxysmal tachycardia showed varying degrees of abnormality in the form of the T waves in the conventional limb and CF leads. No explanation for the T wave changes is offered, but the author discards the possibility that myocardial infarction or quinidine effects were responsible.

WENDKOS.

Gordon, I.: *Mechanism of Lipophage Deposition in Atherosclerosis.* Arch. Path. 44:247 (Sept.), 1947.

The author reviewed and commented on the present knowledge and theories concerning the pathogenesis of atherosclerosis. He believes that Leary's work is the final link in a chain of evidence that began many years ago with the development of alimentary hypercholesteremia in rabbits. After cholesterol ingestion by these animals, the cells of the reticuloendothelial system take up the esterified cholesterol and then become detached, entering the blood stream and infiltrating the intima of the aorta.

Gordon objects to the term "chemotaxis" as an explanation of this infiltrating process, but emphasizes the old physiologic concept of a heavy central cellular concentration with a clear peripheral zone in the circulating column of blood. The endothelial cells filled with cholesterol,

known as lipophages, being lighter than the other blood cells, drift into the clear peripheral zone of the blood column and under the influence of the blood pressure are forced into the intimal structure of the aorta. Localized dilatations of the blood vessel increase this tendency for lighter cells to fall away from the rapidly moving column on to the sides of the vessel. A third factor that would promote this slowing up and drifting process would be eddying of the blood stream.

The physicochemical properties of the lipid-laden lipophages allows for the formation of what might be called a pseudopod, which, first becoming adherent to the intimal surface, becomes the means for the wedging in and entrance of the body of the cell into the intimal structure.

The entrance of the lipoplage into the intima is the earliest sign of aortic atheromatosis. Both Leary and Gordon believe that this lipid material is intracellular from the beginning. The infiltration of these lipid-laden cells beyond the intima finds the first barrier at the internal elastic lamella. Gordon points out that medial infiltration is further impeded by the fact that beyond the internal elastic lamella there is a concentric series of probably sixty-five sheaths of elastic tissue which, together with smooth muscle, constitute the medial structure. The aortic intima, therefore, becomes the depository for the most part of whatever cholesterol-laden cells leave the blood stream. The reason that the aorta is the site of atheromatosis far more than any other blood vessel is that the blood pressure in the aorta is greater than in any other part of the arterial system.

The author does not believe that the capillary blood vessels found in the intima of atheromatous aortas are a causative factor of the atheroma.

He points out in summary that the rabbit feeding experiments with cholesterol bear an authentic relationship to atheromatosis in man inasmuch as all significant human atherosclerosis is associated with hypercholesteremia and an increased number of the circulating lipophages.

GOULEY.

Winder, C. V., and Thomas, R. W.: Cardiovascular and Respiratory Effects of the Anti-Histamine Agent B-Dimethylaminoethyl Benzhydryl Ethel Hydrochloride (Benadryl Hydrochloride). J. Pharmacol. & Exper. Therap. 91:1 (Sept.), 1947.

In the intact dog anesthetized with phenobarbital, benadryl hydrochloride injected intravenously typically elicited a short vascular depression followed by a slight prolonged rise in arterial pressure. This action was not influenced by vagal section or by isolation of the carotid and aortic bodies.

The action of benadryl hydrochloride on the isolated rabbit heart suggests that its action is an intrinsic one upon the myocardium. It causes a variable slight depression in contractions and a fleeting increase in coronary blood flow followed by a more lasting decrease. Respiratory changes, increased rate and decreased depth of respiration, were abolished by vagotomy and carotid denervation.

GODFREY.

Gold, H., Modell, W., Cattell, M., Osenton, J. G., and Cotlove, E. W.: Action of Digitalis Glycosides on the Central Nervous System With Special Reference to the Convulsant Action of Red Squill. J. Pharmacol. & Exper. Therap. 91:15 (Sept.), 1947.

Purified derivatives of red squill, when given to the rat by vein, intramuscularly, or orally, produce a picture which is characteristic. There is an initial brief "shock-like" period (usually only seen with intravenous administration) followed by a period of two to ten hours when the animal appears perfectly normal. Then there is the onset of progressive muscular weakness alternating with periods of violent strychninelike convulsions. The animal dies because of respiratory paralysis during the convulsions. During all of the time following the administration of the drug, the pulse is strong and regular, the heart continues beating after cessation of respiration, and there is no evidence of ventricular fibrillation or other toxic digitalis-like effects on the heart.

The problem that this chain of events presents is whether the convulsant action of red squill is a property of its cardiac glycosides or is due to the action of other impurities. The rat is known to be highly resistant to the cardiac action of the digitalis glycosides in general. Other

digitalis glycosides (digitoxin, gitalin, foleirin, ouabain) produce convulsions in a manner similar to red squill in the rat. The convulsant action appears more highly developed in some glycosides than in others. Convulsions have been observed in species other than the rat (cat and frog) with digitalis glycosides. Derivatives of red squill act like typical digitalis glycosides in the frog, cat, and man. Given intravenously to rats, very large doses of red squill will cause death shortly after its administration. The cause of death is cardiac, the effects resembling those of digitalis poisoning in other species. The convulsant action of red squill, therefore, is due to a peculiarity of both the drug and the species of animal it has been most extensively used in. Many digitalis glycosides have convulsant properties; however, the amount of drug necessary to produce convulsions far exceed the toxic cardiac dose in most species of animals.

GODFREY.

Wollenberger, A.: Metabolic Action of the Cardiac Glycosides. I. Influence on Respiration of Heart Muscle and Brain Cortex. *J. Pharmacol. & Exper. Therap.* 91:39 (Sept.), 1947.

Using slices of guinea pig heart muscle in the presence of glucose or lactate, ouabain, in moderate dosage, was found to produce an increase in oxygen consumption. In high dosage ouabain caused a decreased oxygen consumption. Brain slices (guinea pig) respond similarly, but are one and one-fifth times as sensitive as cardiac muscle. Homogenized brain or heart preparations do not respond to ouabain in moderate dosage with an increased oxygen consumption, nor would intact specimens respond unless an appropriate substitute (such as glucose) was present. If brain slices that had been exposed to ouabain and were actively respiring were washed and placed in a fresh solution, they showed a cessation of respiration.

It is inferred from these findings that ouabain probably works upon the cell surface, increasing permeability to the exogenous substitute; subsequently, the increased permeability causes a loss of some respiratory catalysts.

GODFREY.

York, C. L., and Fischer, W. J. H., Jr.: Plasma Volume Determinations in Rheumatic Subjects During Oral Salicylate Therapy. *New England J. Med.* 237:477 (Sept. 25), 1947.

Seven rheumatic patients were given sodium salicylate orally in dosages sufficient to maintain salicylate blood levels of 35 mg. per 100 cubic centimeters. A plasma volume increase of from 4 per cent to 38 per cent was observed in five of these patients. It was considered probable that this rise was the result of increased sodium ion in the presence of impaired cardiac function. Hematocrit and plasma protein concentration did not consistently reflect the changes in plasma volume. A definite and persistent depression of prothrombin activity usually occurred. Serious hemorrhage occurred in one patient.

KAY.

Fishberg, A. M.: Simulation of Myocardial Infarction by Esophageal Tear. *J. Mt. Sinai Hosp.* 14:296 (Sept.-Oct.), 1947.

The author describes two instances of tear of the esophagus in which the diagnosis of myocardial infarction was considered.

Case 1 is that of a 39-year-old man in whom esophagoscopy disclosed two small lesions about 34 and 35 cm. from the incisor teeth, which were regarded as fibrolipomas. After an evening of drinking he retched and vomited twice, felt agonizing substernal pain, and was given a hypodermic of one-quarter grain of morphine sulfate, followed by three similar injections during the day, with little relief. Oxygen by mask did not help. The initial diagnosis was myocardial infarction. However, two electrocardiograms were negative. Esophagoscopy performed twelve days after admission revealed a transverse tear of the esophagus at a level of 37 centimeters. Exploration of the mediastinum four days later showed enormous dilatation of the lower esophagus, but disclosed no evidence of any extraesophageal lesion. Jejunostomy was performed. After this the patient improved rapidly.

Case 2 is that of a 40-year-old man who was seized with violent pain localized in the upper abdomen and lower anterior chest after a protracted drinking bout during which he vomited repeatedly. The pain became localized in the substernal region and the patient seemed to be going into shock. Myocardial infarction was considered as the likely diagnosis. Later, subcutaneous emphysema appeared in the neck and the chest, which suggested that rupture of the esophagus was probably the diagnosis. The patient sank rapidly. Necropsy showed the posterior surface of the esophagus to be lying in a bed of brownish necrotic material. Section of the esophagus showed a laceration one inch long just above the cardiac portion of the stomach. A second laceration parallel to the first and one-half inch long was also present.

BELLET.

Oppenheimer, B. S., and Zacharias, L.: A Note on the Effect of a Vitamin K-Like Quinone Upon Experimental Renal Hypertension in Dogs. J. Mt. Sinai Hosp. 14:542 (Sept.-Oct.), 1947.

The authors investigated the effect of the water-soluble vitamin K, synkayvite, on five dogs rendered hypertensive by the application of the Goldblatt clamp to the renal arteries. No significant effect in reducing the high blood pressure of these dogs could be observed during or after the administration of this water-soluble vitamin K. The dosage employed in dogs was as follows: 10 mg. for the first two days, 20 mg. for the next six days, and 38 mg. for the next seven days, making a total of 406 mg. injected intramuscularly in fifteen days.

BELLET.

Freis, E. D., and Smithwick, R. H.: The Effect of Lumbodorsal Splanchnicectomy on the Blood Volume and "Thiocyanate Space" of Patients With Essential Hypertension. Am. J. M. Sc. 214:363 (Oct.), 1947.

This investigation was undertaken as a part of a comprehensive study of the effects of sympathectomy on the hemodynamic functions of patients with essential hypertension. It was considered worth while to rule out the possibility that the reduction in blood pressure is accompanied by significant alterations of total blood volume, and, incidentally, to obtain information on the effects of the operation on the intravascular and extracellular fluid compartments of the body.

Repeated blood and "available fluid" ("thiocyanate space") determinations were made on a series of ten cases for periods up to six months following lumbodorsal splanchnicectomy. The total blood volume was reduced in nine cases in the period from eight days to two weeks following operation, due primarily to a diminution in red cell volume. Despite a continued reduction of blood pressure, the total volume was restored to the approximate preoperative level at the end of six months following operation. A slight reduction of the hematocrit value persisted, the deficiency being made up by a compensatory increase in plasma volume. Coincident with the reduction in blood volume noted in the second postoperative week, there was an increase in "available fluid" volume. This elevated value was restored to the preoperative level over a period of several months. Previous observations that the total blood volume is within normal limits in patients with essential hypertension were confirmed. In relation to surface area, the "available fluid" volume of hypertensive subjects was also found to be within the normal range. The reduction in blood pressure following sympathectomy is not dependent upon changes in total blood or "available fluid volume."

DURANT.

Kramer, D. W., and Abramson, E. B.: Fluorescein Studies in Peripheral Vascular Disorders. Am. J. M. Sc. 214:368 (Oct.), 1937.

Eighty-nine patients were studied with fluorescein (4 c.c. of a 20 per cent solution rapidly injected into the antecubital vein) for the appearance time at the lips, hands, and feet. Sixty-five of this series had some form of vascular disease; twenty-four cases presumably had no vascular disease. Various ages and both sexes were represented in the study. The appearance time

in the lips in the nonvascular group was 14.4 seconds and 16 seconds for the patients with vascular disorders. The arm-to-hand time showed an average of 28.5 seconds for the nonvascular cases and 31.2 seconds for the vascular group. The arm-to-foot time ranged from 30 seconds to 3 minutes. However, most of the cases showed an appearance time within 60 seconds; the average for the nonvascular group was 53.4 seconds, with 61.4 seconds for the vascular cases. When the appearance time was beyond 60 seconds, the vascular series predominated over the nonvascular by about 2.5 to 1. Other features which may explain delayed appearance time are old age and cardiac disease. The appearance time is not so easily recognized in the lower extremities and in the Negro. The following figures are suggested for the normal appearance times: arm-to-lip, 12 to 16 seconds; arm-to-hand, 18 to 28 seconds; arm-to-foot, 26 to 61 seconds (average, 53.4). The fluorescein test is superior to those tests which use substances requiring subjective sensations for the end point. The end point with this method is readily recognized. Fluorescein is nontoxic and is readily excreted by the kidneys. Despite the unavailability of a more definite normal standard for arm-to-foot time, the authors were impressed with the delay in appearance time in the lower extremities among patients with known vascular disorders. From this they infer that it gives information relative to the status of the peripheral circulation. It is helpful in deciding and selecting the proper type of ulcer for grafting. It may be of assistance in determining the level for amputation, although the authors have had no personal experience in this respect.

DURANT.

Ferrer, M. I., and Sokoloff, L.: The Antidiuretic Effect of Morphine and Demerol in Congestive Heart Failure. Am. J. M. Sc. 214:372 (Oct.), 1947.

The influence of morphine on mercurial diuresis was studied in nine patients with congestive heart failure. In three, morphine produced an antidiuretic effect. In two patients, demerol also showed an antidiuretic effect. The total chloride excretion during mercurial diuresis was reduced by both drugs. It is suggested that this antidiuretic effect, while probably not operative in all patients, cardiac or otherwise, is of sufficient importance in some cases of cardiac decompensation to account for certain poor results with mercurial diuretics.

DURANT.

Wachstein, M.: Glycogen Storage (Von Gierke's) Disease Predominantly Involving the Heart. Report of a Case With Histochemical Phosphatase Studies. Am. J. M. Sc. 214:401 (Oct.), 1947.

The eighteenth proven case of von Gierke's disease with marked enlargement of the heart is described. On microscopic examination glycogen storage was demonstrable in the cells of various organs, including the brain, the nerve cells in the mesenteric plexus of the intestinal tract, and the Küpffer cells of the liver. The involvement of the Küpffer cells in this case and in the report of Wolff contradicts the conclusion that, in contrast to Gaucher's and Niemann-Pick's disease, the reticuloendothelial system in von Gierke's disease is not ever involved in the abnormal cell metabolism. In the kidneys, no regular distribution within the tubular segments is seen with glycogen disease, whereas in diabetes mellitus, glycogen is found in the terminal segment of the proximal convoluted tubules and to a lesser degree in the ascending limbs of Henle's loop. The histochemical distribution of alkaline and acid phosphatase in the liver, kidney, adrenal, and heart of the author's case was found to be normal, in contrast to previous reports to the contrary. Marked hyperplasia of the Langerhans' islands in the pancreas with preponderance of beta cells was present. It is suggested that this might be due to the increased demand for insulin, related to the abnormally high and persistent rise in blood sugar provoked by the ingestion of carbohydrates in many patients with von Gierke's disease.

DURANT.

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THE III INTER-AMERICAN CARDIOLOGICAL CONGRESS, CHICAGO, JUNE 13-17

The Inter-American Society of Cardiology has authorized the meeting of the III Inter-American Cardiological Congress to be held in Chicago, June 13 to 17, 1948, at the Michael Reese Hospital and at the Stevens Hotel. The Congress is under the auspices of the Society and the National Heart Associations of the Western Hemisphere.

This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting, the week of June 20. Delegates are chosen by the National Heart Associations. Active members in the United States include physicians approved by the American Heart Association.

Physicians wishing to participate in the Congress may obtain an application blank and full information from the Office of the III Inter-American Cardiological Congress, at the Michael Reese Hospital, Chicago. A registration fee of \$15 will be charged. This amount must accompany the application blank, payable to Dr. Richard Langendorf, Secretary-Treasurer of the Congress. Registration must be made not later than April 1.

Each member attending the Congress will be permitted to read in full no more than one paper. This paper must be based on unpublished material. Abstracts, limited to 200 words, must reach the offices of the III Inter-American Cardiological Congress, not later than April 1, 1948.

Additional papers may be submitted to be read by title. If the number of papers exceeds the number which can be accommodated, the President of the Congress will select those to be read in full. The reading time for each paper will be fifteen minutes, including illustrations, with five additional minutes for discussion. However, papers to be presented at the plenary sessions, to be selected by the President of the Congress, will be limited to twenty minutes, with ten minutes for discussion.

Papers submitted will not be published by the Congress. The proceedings and abstracts of communications of the Congress will be published in a special number of the *AMERICAN HEART JOURNAL*. Papers presented at the Congress may be published elsewhere by the authors after the Congress has adjourned. All English abstracts will be translated into Spanish. The Congress office has requested authors to submit their abstracts not only in the original language, but also in the officially authorized translation.

The opening session of the Congress will take place on Sunday afternoon, June 13, at two o'clock, in the Grand Ballroom of the Stevens Hotel. This session will be limited to official addresses of welcome and greetings. Plenary sessions will take place in the North Ballroom of the Stevens Hotel on Monday morning, June 14, and Thursday afternoon, June 17. Ordinary sessions will take place in the Michael Reese Hospital. Two simultaneous meetings will be held in the Rothschild Auditorium and the Sarah Morris Amphitheater. All morning meetings will be held from 9 to 12 o'clock and all afternoon meetings from 2 to 5 o'clock.

A business meeting will be held in the Rothschild Auditorium, Michael Reese Hospital, at 8 o'clock, Thursday evening, June 17.

Hotel and travelling arrangements must be made by members personally. The American Express Company is the official agent for the Congress. Two hundred rooms have been reserved for members of the Congress.

The American Heart Association invites all members of The Congress to attend its Annual meeting, June 18 and 19. The official delegates will be guests at the annual banquet of the American Heart Association.

Chairman of the Honorary Council of the Congress is Dr. James B. Herrick, Chicago, and the Council's United States members include Dr. Henry A. Christian, Boston; Dr. George Dock, Pasadena; Dr. Rudolph Matas, New Orleans; Dr. Paul D. White, Boston; Dr. Carl J. Wiggers, Cleveland; Dr. Frank N. Wilson, Ann Arbor, Michigan.

Officers of the Congress are: Dr. Louis N. Katz, President; Dr. Richard Langendorf, Secretary-Treasurer; and Mrs. Marie Cole de Pardo, Executive Secretary. Vice-presidents from the United States include Dr. Arlie R. Barnes, Rochester, Minn., President of the American Heart Association; Dr. George K. Fenn, President of the Chicago Heart Association; and Dr. Harry A. Durkin, President of the Illinois Heart Association.

The Founder and Permanent Honorary President of the Inter-American Society of Cardiology is Dr. Ignacio Chavez of Mexico City. The Executive President is Dr. Teofilo Ortiz Ramirez of Mexico City. Members of the Board of Directors from the United States include Dr. Barnes, Dr. George R. Herrmann, Galveston, Texas, Dr. William J. Kerr, San Francisco, and Dr. Howard B. Sprague, Boston.

The United States member of the International Council of Cardiology is Dr. Paul D. White, Boston.

NATIONAL HEART WEEK

The greatly enlarged National Heart Week Campaign (February 8-14) of the American Heart Association, which appealed directly to the public for funds for the first time, was reflected in the increased amount of press and radio publicity given to this observance. Possibly the greatest proportional increase in the amount of publicity cooperation was registered in the field of radio. Several popular network programs devoted themselves to extended promotions for the fight against heart diseases.

"Truth or Consequences," which is conducted by Ralph Edwards and sponsored by Proctor and Gamble, and which is heard over the National Broadcasting Company network on Saturday nights, 8:30 to 9:00 P.M., E. S. T., made the American Heart Association the beneficiary of public contributions in its "Walking Man" contest which was continued over a period of many weeks. Paul Whiteman scheduled a "Memory Tune Contest," beginning March 1 on his Monday through Friday record broadcasts over the American Broadcasting Company network at 3:30 P.M., E. S. T., to solicit contributions for the American Council on Rheumatic Fever of the American Heart Association.

Other notable features in the radio phase of the National Heart Week campaign included a broadcast appeal by Hollywood screen actress Ingrid Bergman. Officials of the American Heart Association who broadcast special messages during National Heart Week included Dr. A. R. Barnes, President, who shared a program with Dr. Thomas Parran, Surgeon General of the United States; Dr. H. M. Marvin, Executive Secretary, who was interviewed by Clifton Fadiman; and Dr. Charles A. R. Connor, Medical Director. Federal Security Administrator Oscar Ewing also broadcast a special Heart Week appeal.

Many news and women's commentators devoted time on their broadcasts to appeals for public support in the fight against heart disease, and many commercial network programs included special spot announcements in their regular broadcasts. Magazine articles concerning heart disease appeared preceding, during, and after National Heart Week in such magazines as *This Week*, *Saturday Evening Post*, *Woman's Home Companion*, *American Magazine*, *American Home*, *Newsweek*, *Time*, *Forbes Magazine*, *Look*, *Parent's Magazine*, *The Woman*, *American Mercury*, *Cosmopolitan*, *Pathfinder*, *Hygeia*, and *Science Illustrated*. In addition, magazines published by cooperating trade associations and other organizations published articles and editorials on heart disease. Publications in which these appeared included the *American Legion Magazine*, *The Rotarian*, *The Lion*, and the *American Druggist*.

One of the biggest achievements in the magazine field for the heart disease campaign was the precedent-breaking lead editorial in the January 31 issue of the *Saturday Evening Post* in which the editors for the first time made a specific appeal for funds for the campaign, listing the address to which these funds should be sent. An editorial appeal also appeared in *Collier's*.

Newspaper coverage for National Heart Week was thorough and widespread as a result of the enthusiastic response from feature writers, columnists, syndicates, press associations, and picture services who were acquainted with the facts about heart disease several months before the campaign began.

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Original Communications

CARDIAC OUTPUT IN CONGESTIVE HEART FAILURE

AN ANALYSIS OF THE REASONS FOR LACK OF CLOSE CORRELATION BETWEEN THE SYMPTOMS OF HEART FAILURE AND THE RESTING CARDIAC OUTPUT

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THE function of the heart is to pump blood to the various organs and tissues of the body. When the heart action becomes inadequate, the familiar picture of congestive heart failure develops. Though there has been general agreement that the cardiac output in congestive failure is decreased,¹ it has not been possible to correlate the symptomatology of the patient with the absolute level of the cardiac output. The development of the technique of right heart catheterization has simplified the measurement of the cardiac output in acutely ill patients. The cardiac output is calculated from the Fick principle by dividing the oxygen consumption per minute by the arteriovenous oxygen difference. Arterial blood is obtained from any convenient artery by direct puncture and mixed venous blood is obtained by the catheter from the pulmonary artery, right ventricle, or right atrium. With this new tool, it seemed worthwhile to reinvestigate the relation between the cardiac output and the symptoms of congestive failure.

METHOD

The right heart was catheterized via the median antecubital vein.²⁻⁴ The oxygen content of the mixed venous blood was determined on samples collected from the pulmonary artery, right ventricle, or right atrium. The mean atrial pressure was recorded in centimeters of saline, a point 5.0 cm. below the fourth costochondral junction being taken as reference point. Samples of arterial blood

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were obtained from the brachial or femoral artery, and the arterial pressure was recorded by the method of Hamilton and associates.⁵ The oxygen content of the blood was determined by the method of Van Slyke.⁶ The oxygen consumption per minute was determined by collecting the expired air for two- or three-minute periods and analyzing a sample for oxygen by the method of Haldane.⁶ The cardiac output is recorded as liters per minute. The cardiac index is the cardiac output per liter per minute per square meter of body surface. Heparin was used as the anticoagulant for determining the hematocrit reading. The total protein concentration was measured by the falling drop method.

RESULTS

Normal Subjects.—The cardiac output was measured sixty-six times in sixty-one normal subjects. The determinations were done in the morning with the subject in the recumbent position and after a twelve-hour fast. Subjects who had a hemoglobin concentration below 10 Gm., or a hematocrit reading below 25, or who had evidence of heart or lung diseases were not included. Otherwise, there was no selection. The subjects were doctors and medical students working in the hospital, and patients convalescing from elective surgery or respiratory infections. The relevant data on these subjects are given in Table I. No difference was apparent in the values for cardiac output in the convalescent patients and the hospital personnel. Every effort was made to keep the subjects comfortable and to relieve apprehension. While subjects who had shown signs of anxiety previous to the time of catheterization were not selected, no subject was excluded from this series because he showed evidences of anxiety during the test, as we were interested in establishing the range of cardiac output which would be found in sixty-six consecutive determinations on normal subjects. The average arteriovenous oxygen difference was 4.1 volumes per cent and the average cardiac index was 3.6. These values are not significantly different from those previously reported for a smaller group of normal subjects who showed no evidence of anxiety. While a few subjects in the series reported here had very high cardiac indices because of their emotional reaction to the test, they were in the distinct minority and did not significantly modify the average values.

Patients With Congestive Heart Failure.—The cardiac output was measured fifty-four times in forty-eight subjects in congestive failure (Table II). The determinations were usually done in the morning after a twelve-hour fast. A few patients were studied immediately after admission to the hospital. These patients had usually been too sick to eat much food during the day of admission and there was no difference in the results in these patients. If the patient was uncomfortable in the recumbent position, the trunk was supported at a 30° angle by a back rest. Patients were not included in this series unless the hemoglobin concentration was above 10 Gm. and the hematocrit reading above 25. Patients with thyrotoxicosis or arteriovenous fistulas were excluded.

The cardiac output in the patients with heart failure was lower than in the normal subjects. There was much less overlap than was anticipated. The cardiac output was below 4.5 liters per minute in forty-two, or 78 per cent of the de-

terminations in patients with heart failure. It was above 4.5 liters in fifty-four, or 82 per cent of the determinations in normal subjects.

The age distribution of the normal and cardiac subjects was not comparable. There were many more normal subjects between the ages of 20 and 30 years and few were older than 40. In the age group between 29 and 40 years, there were twenty-one normal subjects and eighteen cardiac patients. A comparison of the values for cardiac output in these two small groups with relatively comparable ages shows the same differences between the normal subjects and the patients with congestive failure that were evident in the groups as a whole.

As the cardiac patients had varying amounts of edema and many of them never became edema-free, the true surface area could not be calculated with any exactness. The surface area was calculated from the patient's height and from his weight at the time of the observations. To eliminate the factor of edema, the cardiac outputs were plotted against height in normal and cardiac subjects. The results obtained were similar to those found by plotting against surface area.

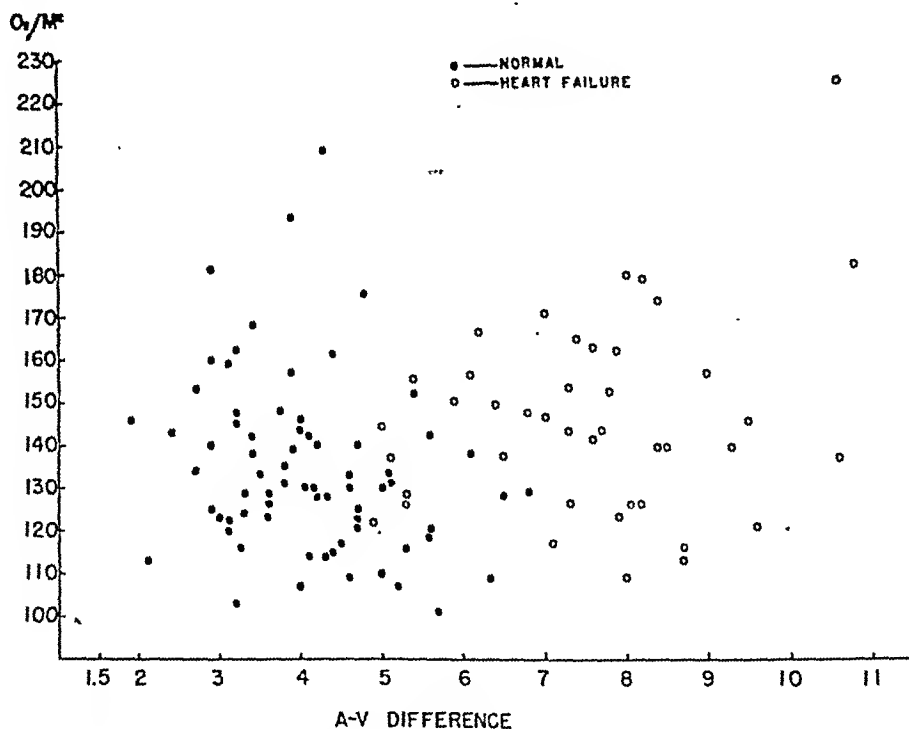


Fig. 1.—Relation between oxygen consumption and arteriovenous oxygen difference in normal subjects and patients with congestive heart failure.

The arteriovenous oxygen difference gives a rough index of the relationship between the metabolic demands of the body and the efficiency of the circulation. In the patients with congestive heart failure, the arteriovenous oxygen difference was greatly increased. Forty-eight, or 89 per cent, of the determinations in patients with failure had an arteriovenous oxygen difference greater than 5.2 volumes per cent. Only nine, or 14 per cent, of the determinations in normal subjects showed an arteriovenous oxygen difference greater than 5.2 volumes per cent. (Fig. 1).

TABLE I. DATA ON CIRCULATION IN NORMAL SUBJECTS. DETERMINATIONS WERE MADE IN MORNING AFTER TWELVE-HOUR FAST. SOME SUBJECTS WERE NOT RELAXED AS SHOWN BY HIGH OXYGEN CONSUMPTION, RAPID PULSE RATE, AND ELEVATED SYSTOLIC PRESSURE

SUBJECT	AGE (YR.)	SEX	SURFACE AREA (SQUARE METERS)	HEIGHT (IN.)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQUARE METER)	ARTERIO-VEINOUS OXYGEN DIFFERENCE (VOLS. PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)
C. A.	23	M	1.88	71	138	3.9	6.6	3.5
J. A.	33	M	1.94	71	168	3.4	9.6	4.9
R. A.	22	F	1.76	69	148	3.7	7.0	4.0
C. B.	23	M	1.90	73	123	3.0	7.8	4.1
W. B.	27	M	1.76	73	143	2.4	10.5	6.0
H. B.	26	M	1.99	73	147	3.2	9.1	4.6
E. C.	14	M	1.76	70	120	5.6	3.8	2.2
O. F.	41	F	1.55	63	131	5.2	3.9	2.5
M. H.	39	F	1.91	70	124	4.7	5.0	2.6
B. J.	39	M	1.86	68	128	3.6	6.5	3.5
I. L.	29	F	1.63	64	125	2.9	7.0	4.3
N. P.	37	F	1.59	64	113	2.1	8.6	5.4
S. S.	35	F	1.59	63	123	3.6	5.4	3.4
W. M. S.	44	F	1.73	66	114	4.1	4.8	2.8
J. W.	42	M	1.68	66	152	5.4	4.7	2.8
E. W.	58	F	1.60	63	133	4.6	4.6	2.9
W. A.	23	M	1.86	70	116	5.3	4.1	2.2
J. B.	30	M	2.04	71	140	4.2	6.8	3.3
J. S.	30	M	1.75	68	122	4.7	4.5	2.6
V. M.	18	M	1.77	66	145	3.2	8.0	4.5
O. F.	31	M	1.87	71	129	6.8	3.6	1.9
A. R.	40	M	1.87	73	175	4.8	6.8	3.6
T. B.	23	M	1.88	71	119	5.6	3.9	2.1
H. A.	21	M	1.77	71	157	3.9	7.1	4.0
L. H.	38	M	1.69	68	117	4.5	4.4	2.6
L. H.					107	4.0	4.5	2.7
J. A. J.	32	M	1.87	71	133	5.1	4.8	2.6
J. H.	30	M	1.58	61	209	4.3	7.7	4.9
J. A. H.	19	M	1.82	71	134	2.7	9.0	4.9
E. A.	30	M	1.81	68	142	3.4	7.7	4.2
N. A.	33	M	1.75	70	130	4.6	5.0	2.9
L. R.	22	M	1.95	72	116	3.3	6.9	3.5
J. B.	36	M	2.00	69	127	3.6	7.1	3.6
L. L.	16	M	1.73	68	142	5.6	4.4	2.5
W. W.	57	M	1.73	66	129	4.2	5.3	3.1
F. W.	23	M	1.98	72	106	5.7	3.8	1.9
M. S.	22	M	1.68	68	128	6.5	3.4	2.0
J. P.	22	M	1.80	70	110	5.0	4.0	2.2
C. G.	22	M	1.73	68	124	3.3	6.6	3.8
W. F.	24	M	1.81	69	107	5.2	3.6	2.1
*E. S.	35	M	2.04	73	109	4.6	4.9	2.4
*W. M.	23	M	1.90	71	103	3.2	6.1	3.2
*W. M.					120	3.1	7.4	3.9
*W. L. M.	22	M	2.04	73	121	4.7	5.3	2.6
*C. G.	22	M	1.91	74	131	3.8	6.5	3.4
*W. S.	25	M	2.04	73	133	3.5	7.7	3.8
*W. F.	23	M	1.85	71	114	4.3	4.9	2.7
*M. S.	22	M	1.87	70	130	5.0	4.9	2.6
*R. G.	23	M	1.98	72	129	4.2	6.1	3.1
*W. B.	23	M	1.93	71	146	1.9	14.8	7.7
*W. B.					122	3.1	7.6	3.9

TABLE I. DATA ON CIRCULATION IN NORMAL SUBJECTS. DETERMINATIONS WERE MADE IN MORNING AFTER TWELVE-HOUR FAST. SOME SUBJECTS WERE NOT RELAXED AS SHOWN BY HIGH OXYGEN CONSUMPTION, RAPID PULSE RATE, AND ELEVATED SYSTOLIC PRESSURE—CONTINUED

SUBJECT	AGE (YR.)	SEX	SURFACE AREA (SQUARE METERS)	HEIGHT (IN.)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQUARE METER)	ARTERIO-VEINUS OXYGEN DIFFERENCE (VOLS. PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)
*L. M.	30	M	1.84	67	138	6.1	4.2	2.3
*B. J.	25	M	1.99	71	140	4.7	5.9	3.0
*H. B.	26	M	1.99	73	159	3.2	9.9	5.0
*J. C.	16	M	1.69	70	130	4.1	5.4	3.2
*P. M.	17	M	1.78	67	143	4.0	6.4	3.6
*C. L.	33	M	1.77	69	135	3.8	6.3	3.6
*S. L.	27	M	1.76	67	129	3.3	6.8	3.9
*G. H.	39	M	1.93	70	130	4.1	6.3	3.3
*J. F.	27	M	1.63	65	146	4.0	6.0	3.7
*Y. W.	25	M	1.82	70	138	3.4	7.4	4.1
*W. P.	32	M	1.74	65	162	3.2	8.8	5.1
*W. P.					153	2.7	9.9	5.7
*W. P.					142	4.1	6.0	3.4
*J. T.	31	M	1.84	69	181	2.9	11.5	6.2
*I. R.	22	M	1.84	68	160	2.9	10.2	5.5

*Data reported in J. Clin. Investigation 24:326, 1945.

The degree of dyspnea and orthopnea and the atrial pressure reading varied greatly in this series, depending upon whether salt had been restricted in the diet and a mercurial diuretic administered. These patients were either in chronic heart failure, requiring salt restriction and the biweekly administration of a mercurial diuretic to remain comfortable, or they were new admissions to the hospital who were studied before therapy. In general, the group was composed of patients with severe heart failure.

The atrial pressure, arterial pressure, and pulse rate could not be correlated with the symptoms or with the cardiac output. The etiology of the heart disease made no difference in the findings. Equally severe reductions in cardiac output were found in all of the common types of heart disease (Table I).

Response to Lanatoside C.—Patients with congestive failure who had not been receiving digitalis were given 1.6 mg. of lanatoside C intravenously. This produced a decrease in arteriovenous oxygen difference, an increase in cardiac output, and a rapid fall in atrial pressure which was not dependent on a change in blood volume. The amount of subjective relief which occurred in the first hour after the drug was given was quite variable. Regardless of the rise in cardiac output, the patients always remained dyspneic and orthopneic, though in some these symptoms were less marked. These observations will be reported in detail elsewhere. At present, it is sufficient to emphasize that symptoms of dyspnea and orthopnea persisted after the cardiac output was increased by lanatoside C. The

TABLE II. STUDIES OF THE CIRCULATION IN PATIENTS WITH CONGESTIVE HEART FAILURE

PATIENT	AGE (YRS.)	SEX	SURFACE AREA (SQ. METER)	HEIGHT (IN.)	OXYGEN CONSUMPTION (ML. PER MIN. PER SQ. METER)	ARTERIAL OXYGEN SATURATION (PER CENT)	ARTERIAL OXYGEN CONTENT (VOLUMES PER CENT)	MIXED VENOUS OXYGEN CONTENT (VOLUMES PER CENT)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOLUMES PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQ. METER)	ARTIAL PRESSURE (MM. H ₂ O)	ARTERIAL PRESSURE (MM. HG)			HEART RATE (BEATS PER MIN.)	HEMOGLOBIN (GML. PER 100 C.C.)	HEMATOCRIT READING (PER CENT)	TOTAL PROTEIN (GML. PER 100 C.C.)	DIAGNOSIS
													SYSTOLIC	DIASTOLIC	MEAN					
M.R. 11-8-43	45	M	1.58	65	141	91	18.9	11.3	7.6	2.9	1.8	15	164	60	93	94	14.1		5.3	SAI
2-24-41			1.66		139		14.5	6.0	8.5	2.7	1.6		190	70	105	96	12.1	52.0	6.1	IHD
K.Mc.	49	F	1.94	68	155		18.8	13.4	5.4	5.6	2.9	112	200	100	70	75	15.9	39.0	5.3	IHD
V.L.	14	F	1.34	62	164	94	13.7	6.3	7.4	3.0	2.2	200	105	58		100	11.4			
M.B. 12-3-43	33	M	2.08	75	122	91	18.9	14.0	4.9	5.2	2.4	25	184	124	145	88	14.5	54.0		IHD
12-31-43			2.19		150	93	13.7	7.9	5.8	5.7	2.6	295	203	122	148	79	11.0	47.0		
4-15-44			2.28		126		16.3	8.2	8.1	3.5	1.5	300	197	128	150	79	13.2			
L.L.	51	F	1.63	64	147		13.4	6.6	6.8	3.5	2.1	110	202	118	139	79	11.7	40.0		IHD
J.D.P.	32	M	2.04	78	137		16.3	9.8	6.5	4.3	2.1	70	140	98	110	107	13.5	45.0	7.0	IHD
E.L.	68	F	1.53	63	139	80	15.6	6.3	9.3	2.3	1.5	140	162	88	109	100	13.9	53.5		IHD
L.H.	41	M	1.91	71	149	79	13.7	7.3	6.4	4.4	2.3	195	116	72	80	104	12.3	41.8	3.8	RHD-MS HHD and AHD
J.R.	63	F	1.47	62	137		16.1	5.5	10.6	1.9	1.3		192	94		88				
F.M.	51	M	1.96	66	173	81	13.9	5.5	8.4	4.0	2.0	250	208	133	155	86	12.7	41.2		IHD
E.M.	56	M	1.56	64	156		16.5	10.4	6.1	4.0	2.6	30	124	60		94	12.2	31.3		RHD-MS
A.H.	62	F	1.55	64	126		13.5	8.2	5.3	3.7	2.4	95	174	64	100	88	11.3	36.0	5.3	SAI
C.P.	43	F	1.80	64	113	94	14.7	6.0	8.7	2.3	1.3	185	102	82	83	178	11.9	38.0		Parex. aur. tachy.
A.W.	58	M	2.10	70	145	90	17.2	7.7	9.5	3.2	1.5	220	137	100	108	112	13.5	47.0	5.0	AHD
J.H.	42	M	1.92	71	182		16.6	5.8	10.8	3.2	1.7	150	202	73	112	84	13.9	44.0		SAI
N.J.	39	F	2.21		179		12.5	4.5	8.0	4.9	2.2	300	195	87	126	112	11.5	26.0	6.7	RHD-MS
W.F.	48	M	1.82	71	143		16.0	8.3	7.7	3.4	1.9	245	168	78	114	88	10.9			SAI
A.J.	37	M	2.12	67	178		18.8	10.6	8.2	4.6	2.2	150	175	107	133	88	15.6	51.0		IHD
E.M.	33	M	1.96	67	153		15.1	7.8	7.3	4.1	2.1	270	158	97	119	111	12.5	46.4		IHD
W.A.	26	M	2.04	64	152		16.1	8.3	7.8	4.0	2.0	50	175	120	137	84	13.2	42.0		IHD
C.Mc.	63	M	1.82	66	166		15.2	9.0	6.2	4.9	2.7	135	200	130	152	94	12.8	41.8		IHD
H.M.	34	M	1.96	71	146		16.2	9.2	7.0	4.1	2.1	125	142	48	87	120	12.7	44.0		SAI
S.H.	45	F	1.94	68	144		14.3	9.3	5.0	5.6	2.9	140	131	75	89	104	11.9	41.0	6.2	RHD-MS

J. C.	54	M	1.58	65	161		15.2	7.3	7.9	3.2	2.0	60	200	44	89	79	11.4	37.0	5.7	SAI
W. L.	47	M	1.65	64	137		15.1	9.9	5.2	4.3	2.6	35	112	46	72	84	13.1	38.0	5.5	SAI
S. J.	33	M	1.77	65	170	71	10.6	3.6	7.0	4.3	2.4	160	115	75	87	100	11.8	38.0	5.3	Unknown
H. H.	46	M	2.00	72	225		16.7	6.1	10.6	4.2	2.1	160	265	86	151	100		48.0		SAI
F. P.	33	M	1.77	65	128		13.5	8.2	5.3	4.3	2.4	50	185	102	123	88	11.1	41.0	5.4	AHD
J. J.	30	M	1.75	67	121	92	15.0	5.4	9.6	2.2	1.3	215	137	97	105	52	12.1	42.8	5.9	RHD-MS
L. P.	39	M	1.96	73	117		20.2	13.1	7.1	3.2	1.6						15.5	50.0		RHD-MS
A. P.	40	M	1.90	72	109	85	14.4	6.4	8.0	2.6	1.4	290	89	66	69	104	11.8	42.0	4.2	AHD
R. W.	49	M	1.90	68	126		14.9	7.6	7.3	3.3	1.7	120	147	102	114	104	12.1	39.0	5.4	AHD
M. W.	56	F	1.75		139		14.8	6.4	8.4	2.9	1.7	130	139	87	100	88	12.8	40.3	4.9	RHD-MS
J. M. L.	34	F	1.56	61	156		16.4	7.4	9.0	2.8	1.8	210	188	36			13.6			RHD-MS
12-7-43			1.64		126		15.2	7.1	8.1	2.6	1.6	210	183	43	85	64	12.6	40.0		RHD-MS
7-11-45			1.69	66	162		14.1	6.5	7.6	3.1	1.8	245	212	51	97	94		40.0	5.7	SAI
W. S.	40	M	2.42	69	143		22.8	15.5	7.3	4.7	1.9	205	183	101	127	94	18.1	47.8	4.9	IHD
J. M.	54	M	1.91	68	116		14.6	5.9	8.7	2.5	1.3		178	66	99		10.6	39.5		SAI
A. M. W.	36	F	1.85		123		14.4	6.5	7.9	2.9	1.6	215	108	80	86	120	11.5	38.0	3.7	RHD-MS
T. S.	54	M	1.70	66	125		17.9	11.7	6.2	3.4	2.0		150	80				46.8	6.1	SAI
H. S.	37	M	1.61	66	160	94	17.5	11.1	6.4	4.0	2.5	6	148	94				40.8	6.5	HHD
J. G.	63	M	1.61	66	201	91	14.2	8.3	5.9	5.5	3.4		150	60				35.2	6.3	SAI
L. V. E.	41	M	1.86	66	184	96	16.4	8.6	7.8	4.4	2.4	22	170	100				42.0	5.3	HHD
I. D.	64	F	1.55	65	163	93	17.1	10.5	6.6	3.8	2.5	6	220	80				43.8	5.8	HHD and RHD-MS
L. B.	52	M	2.00	73	141		12.9	5.4	7.5	3.8	1.9	70	135	60	78	88	10.1	36.6	4.3	SAI
J. C.	32	M	1.64	69	129		14.1	10.9	3.2	6.6	4.0	0	148	44	70	91	12.3	43.0	4.0	SAI
G. H.	57	M																		
T. T.																				
2-27-44	37	F	1.45	64	128		16.9	9.1	7.8	2.3	1.6	185	206	117	143	88	12.0	38.0	6.5	HHD
12-23-44			1.56		154		15.5	5.2	10.3	2.3	1.9	295	206	141	163	94	11.2	39.2	6.8	
10-9-46	40		1.64		144		16.5	12.2	4.3	5.9	3.6		160							
L. F.	35	F	1.44	64	131	76	14.5	7.5	7.0	2.7	1.9	170	156	34	64	71		38.5		SAI
G. D.	55	M	1.88	66	125		11.7	6.5	5.2	4.5	2.4	18	197	54	92	68	11.5	37.1	6.2	SAI

SAI—Syphilitic aortic insufficiency.

HHD—Hypertensive heart disease.

RHD—Rheumatic heart disease.

MS—Mitral stenosis.

AHD—Arteriosclerotic heart disease.

disappearance of the dyspnea was dependent on the relief of pulmonary edema. It takes some time for the wet lungs to become dry even though the cardiac output in certain instances may be brought quickly to an adequate level by digitalis.

Patients With Congestive Heart Failure and Severe Anemia or Thyrotoxicosis.—Observations were made on two patients with severe anemia and heart failure. One was anemic because of severe menorrhagia, and the second because of renal failure. The atrial pressure was greatly increased and dyspnea, orthopnea, and edema were marked. The cardiac outputs were considerably higher than would have been expected in a normal subject of the same size and height (Table III). Similar observations were recorded in two patients with thyrotoxicosis and heart failure Table (III). Both severe anemia and thyrotoxicosis cause a great increase in the cardiac output under basal conditions. It is to be expected, therefore, that congestive failure might develop long before the resting output fell to the level found in normal subjects.

DISCUSSION

The occurrence of high atrial pressure and congestive failure in the presence of an elevated cardiac output in the patient with anemia or thyrotoxicosis is of considerable interest. We have pointed out before that the damming back of blood behind the right ventricle because of heart failure is not an adequate explanation for the rise in venous pressure.⁷ Since the blood circulates in a closed system, the left ventricle can pump to the right ventricle only the blood which has been pumped to it by the right ventricle plus that amount of blood which can be delivered to the left ventricle, independent of the right ventricle, by active vasoconstriction in the lungs. There is no evidence that vasoconstriction in the lungs can push any large amount of blood into the systemic circulation. The rise in venous pressure in these patients appears to be related to the increased blood volume which occurs in chronic congestive failure and to venoconstriction which occurs in the presence of an inadequate output of the left ventricle. The possible explanations for such venoconstriction have been recently summarized by Merrill and associates.⁸

The cardiac output of normal subjects is increased above the normal resting level by work and by apprehension.^{4,11} Which of these factors is at work to increase the cardiac output can frequently be determined by observing the oxygen consumption and arteriovenous oxygen difference.¹¹ Work results in a sharp increase in oxygen consumption and a slight widening of the arteriovenous oxygen difference. Apprehension results in a considerable decrease in arteriovenous oxygen difference and a smaller rise in oxygen consumption. When the oxygen consumption per square meter is plotted against the arteriovenous oxygen difference (Table I), it is apparent that increased oxygen consumption in the normal subjects is associated with a marked decrease in arteriovenous oxygen difference, indicating that these subjects were apprehensive. In the patients with cardiac failure, high levels of oxygen consumption were associated with large arteriovenous differences (Table II), indicating that the circulation was inadequate for the

TABLE III. HIGH CARDIAC OUTPUT IN CONGESTIVE FAILURE WITH SEVERE ANEMIA AND THYROTOXICOSIS

SUBJECT	AGE (YR.)	SURFACE AREA (SQUARE METERS)	OXYGEN CONSUMP- TION (ML. PER MIN. PER SQUARE METER)	ARTERIAL OXYGEN CONTENT (VOLS. PER CENT)	VENOUS OXYGEN CONTENT (VOLS. PER CENT)	ARTERIO- VENOUS OXYGEN DIFFER- ENCE (VOLS. PER CENT)	CARDIAC OUTPUT (LITERS PER MIN.)	CARDIAC INDEX (LITERS PER MIN. PER SQUARE METER)	ATRIAL PRESSURE (MM. OF H ₂ O)	HEMATO- CRIT READING	DIAGNOSIS
B. S.	46	1.8	143	2.8	1.3	1.5	17.0	9.4	200	9	Anemia from menorrhagia Hypertension and uremia Thyrototoxicosis Thyrototoxicosis
A. M.	39	1.38	138	6.3	3.2	3.1	6.1	4.5	225	16	
P. W.	55	1.44	202	12.8	9.4	3.4	8.6	6.0	155	42.4	
N. H.	39	1.53	255	10.1	7.1	3.0	8.5	5.6	250	33	

metabolic needs of the body at the time of the study. The abnormally large arteriovenous oxygen difference at rest is probably a better indication of the actual inadequacy of the circulation than is the absolute level of the cardiac output.

The finding of a reduced cardiac output in patients with uncomplicated congestive heart failure agrees with the results of other investigators using the Fick principle. McGuire and collaborators⁹ obtained blood from the heart of several patients by direct puncture. The South American investigators² obtained blood from the right atrium by cardiac catheterization. Harrison¹ and Stewart and Cohn,¹⁰ using the acetylene method, found a reduced cardiac output and an increased arteriovenous oxygen difference in patients with moderately severe congestive failure.

It is rather surprising to find such uniform agreement among the various investigators who have measured the cardiac output in congestive failure. The conditions under which the data are collected are such as to minimize the differences between a normal and a failing circulation. The cardiac subject at rest in the basal state may have an entirely normal output and still have easily demonstrable circulatory failure on mild exertion.¹² The reserve in the cardiovascular system is in the direction of increasing the cardiac output. The output does not have to be reduced far below the resting level to produce signs of circulatory failure in the normal subject.

While there is general agreement that the cardiac output in congestive failure is reduced, there has been less agreement as to the relation between the reduction of cardiac output and the symptoms of heart failure. Most investigators have found no constant relationship between the absolute level of the cardiac output and the presence of dyspnea, orthopnea, and edema. Our findings are similar.

This lack of correlation between the absolute level of the cardiac output and the symptoms of failure is shown most strikingly in the data collected on the patients with heart failure complicated by anemia and thyrotoxicosis. The patient with severe anemia and heart failure will have a high cardiac output at rest in the presence of all the usual signs and symptoms of severe congestive heart failure. If his anemia is controlled, the cardiac output will decrease and the signs of failure will disappear. This same sequence of a high cardiac output with failure and a low cardiac output with compensation is seen in heart failure produced by thyrotoxicosis. The thyrotoxic patient with failure has a high output at rest, but because it is not high enough to satisfy the needs of his increased metabolism, failure occurs. If the hyperthyroidism is satisfactorily treated, the requirements of the body for blood are greatly decreased. The cardiac output falls to a normal level, but the output is now adequate for the body needs and compensation occurs.

At first, the concept that certain patients develop congestive failure with a high cardiac output and compensate with a smaller cardiac output appears strange. A little reflection leads us to the conclusion that this is a common occurrence. The cardiac output during the usual daily working routine is considerably

elevated over the basal level. Most patients develop failure during activity. At that time the cardiac output is above the resting level but is inadequate for the needs of the active patient. On resting the cardiac output falls as in a normal subject. With the reduction of the need for blood the output is now adequate, and the subject compensates with an output considerably lower than that present while he was decompensating.

The restless, dyspneic, ill patient with failure may have an abnormally large requirement for blood as demonstrated by a high arteriovenous oxygen difference in the presence of an output equal to that of a normal resting subject. If the water logging of the lungs is relieved by sodium restriction and if the patient becomes quiet and is able to breathe normally, the patient may remain compensated at rest with the same cardiac output as on admission. That compensation at rest has occurred may now be demonstrated by the fact that the patient can eat large amounts of salt without forming excessive edema. If the apprehension and restlessness on admission were particularly severe, he may remain compensated at rest with an even lower output than he had on admission.

The symptoms due to retention of fluid in the lungs may persist after the output has become adequate. For example, a patient treated with digitalis may quickly increase his cardiac output to a level adequate to cause a rapid diuresis. Nevertheless, many of the symptoms of waterlogged lungs will remain until the kidneys have removed the retained salt and water.

If the cardiac output is measured at rest the following combinations may be expected to exist:

1. Cardiac output low with failure; remains low with the disappearance of symptoms. Symptoms will be relieved by sodium restriction and continued use of diuretics. Majority of patients reported in this paper fall into this classification.
2. Cardiac output low with failure, increases with administration of digitalis or when such complications as pulmonary infarctions clear up. Does not require salt restriction or diuretics when activity is reduced by bed rest.
3. Cardiac output normal with failure; remains normal on compensation. Decompensation develops with increased activity. Cardiac output adequate at rest; symptoms at time of study present because of waterlogging of the lungs, which will persist until diuresis is completed.
4. Cardiac output high with failure; falls with compensation. This combination is present in (a) restless, apprehensive, dyspneic patients whose output is adequate for rest but inadequate for apprehension and mild exertion and (b) patients with hyperthyroidism, anemia, arteriovenous fistulas, patent ductus arteriosus, beriberi, and certain infections.

Thus, it appears that symptoms of congestive failure develop whenever the cardiac output is inadequate for the demands of the tissues over a prolonged period of time and that there is no absolute level of cardiac output at which the symptoms of congestive failure appear.

The finding that there is no close correlation between the level of the cardiac output and the presence of dyspnea or orthopnea has led to the concept that these symptoms are only indirectly related to the level of the cardiac output.¹ The dyspnea and orthopnea are related to the waterlogging of the lungs, and anything which relieves the edema of the lungs will improve these symptoms even though the cardiac output remains inadequate. Why does waterlogging of the lungs occur in heart failure?

Merrill¹³ has shown that an inadequate cardiac output is associated with a reduced renal blood flow and a reduced glomerular filtration rate. This may occur at any level of cardiac output. In patients with heart failure who are exercising and in patients with heart failure with thyrotoxicosis, the cardiac output may be increased above the basal level but still be inadequate for the needs of the body.¹⁴ This will be reflected by a striking reduction in renal blood flow. He believes that in cardiac failure salt and water are retained because the sodium conserving function of the tubules causes them to reabsorb the majority of the reduced amount of sodium presented to them in the glomerular filtrate. Some factor other than sodium retention by the kidney must account for the marked tendency of the cardiac patient to localize the retained fluid in the lungs. It is believed that high pulmonary venous and capillary pressures, due to failure of the left ventricle, account for the fact that so much of the sodium and water retained by the kidney localizes in the lungs and that the dyspnea and orthopnea are symptoms produced by this edema. The waterlogged lungs may be treated by sodium restriction and the use of diuretics. This relieves the symptoms without altering the circulation. They may be treated by increasing the cardiac output by digitalis. This improves the circulation to the kidneys and causes a diuresis. They may be treated by correcting such complications as anemia and hyperthyroidism, thus decreasing the demands of the tissues for blood and making the cardiac output adequate.

SUMMARY AND CONCLUSIONS

1. The cardiac output was measured at rest after a twelve-hour fast in normal subjects and in patients with severe congestive failure. The cardiac output was less than 4.5 liters per minute in 78 per cent of the determinations in patients with failure. It was above 4.5 liters per minute in 82 per cent of the determinations in normal subjects.

2. In two patients with severe anemia and in two patients with hyperthyroidism, the cardiac output was greatly increased above the normal value in the presence of congestive failure. These patients demonstrate that there is no absolute level of cardiac output at which congestive failure develops. The cardiac output was increased, but not to a level adequate for the requirements of the body. Congestive failure occurs whenever the output of the heart is inadequate for the needs of the tissues over a long period of time.

3. Dyspnea and pulmonary congestion are caused by waterlogging of the lungs. The degree of edema in the lungs depends on (a) the height of the pulmonary capillary pressure produced by the left ventricular failure and (b) the amount of salt and water retained by the kidneys. Salt restriction in the diet may lessen

pulmonary congestion without altering the circulation. Because of the many variables involved, there is no close relation between the symptoms of heart failure and the cardiac output.

4. If the cardiac output is measured at rest, the following combinations may be expected to exist:

A. Cardiac output low with failure; remains low with the disappearance of symptoms. Symptoms are relieved by sodium restriction and continued use of diuretics. Majority of patients reported in this paper fall into this classification.

B. Cardiac output low with failure; increases with administration of digitalis or when such complications as pulmonary infarctions clear up. Does not require salt restriction or diuretics when activity is reduced by bed rest.

C. Cardiac output normal with failure; remains normal on compensation. Decompensation develops with increased activity. Cardiac output adequate at rest; symptoms at time of study present because of waterlogging of the lungs which will persist until diuresis is completed.

D. Cardiac output high with failure; falls with compensation. This combination may be shown by (1) restless, apprehensive, dyspneic patients whose output is adequate for rest but inadequate for mild exertion; and by (2) patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi, and certain infections.

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CONCEALED A-V CONDUCTION: THE EFFECT OF BLOCKED IMPULSES ON THE FORMATION AND CONDUCTION OF SUBSEQUENT IMPULSES

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AN INFREQUENT phenomenon which amplifies the physiology of impulse conduction and impulse formation is the effect of concealed A-V conduction. Under these circumstances, an impulse manifests its effect by altering the transmission or timing of subsequent beats without being manifest electrically itself.

In 1894, Engelmann¹ stated that every effective stimulus applied to the auricle, even if it is not followed by a ventricular response, lengthens the succeeding A-V interval. The actual mechanism to account for this effect was investigated much later. In 1925, Ashman² studied the influence of blocked impulses on subsequent conduction in compressed auricular muscle of the turtle heart. He observed that the earlier the blocked impulse follows a transmitted one, the less is its effect upon the conduction time of a subsequently transmitted impulse; and, conversely, the later the blocked impulse follows the transmitted one, the greater is its effect upon subsequent conduction. Drury and Andrus³ investigated the effects of hydrogen ion concentration upon the muscle of the dog's auricle perfused with Locke's solution, and were able to show that a condition comparable to that termed decrement arises when oxygen-free perfusates of pH 7.0 are used. The condition is one in which an impulse is found to slow down to a halting point in its course through the affected muscle. Similarly, Drury⁴ in his observations upon intra-auricular block produced by pressure or cooling stated that "the excitation waves fail to pass through compressed muscle, not because they reach irresponsive muscle, but because they fade away as they travel." In his investigation of 2:1 block, he presented evidence that the alternate (blocked) impulses enter the damaged region and deprive it of the rest period which it obtains when the rate is halved. Lewis and Master⁵ in their classical observations upon A-V conduction in the mammalian heart demonstrated clearly that in 2:1 A-V block, whether produced by raising the auricular rate, by stimulating the vagus, or by poisoning with quinidine or the products of asphyxia, the conduction intervals are lengthened by the presence of the alternate auricular beats, that is, those to which the ventricle fails to respond. They defined the "phase of interference" as that period of the cycle during which an impulse which fails to be conducted from auricles to ventricles nevertheless influences the passage

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of the succeeding impulse, postponing or preventing the ventricular response. The phase of interference was found to begin immediately after the period which can be regarded as corresponding to the absolute refractory state of the A-V tissues, and it is operative until conduction from auricles to ventricles occurs. The phase of interference is brief, occupying 0.02 to 0.09 second in the dog's heart. When an auricular impulse falls within this phase, it is conveyed into the conducting tissues but does not traverse them. The impulse so conveyed affects the rest period of those portions of the conducting tissues which the impulse reaches, and in this manner lengthens the next conduction interval. Lewis and Drury,⁶ in revising the views of the refractory period, stated that "when the impulse falls early, the response or nonresponse of the A-V tissues is gauged, not by response or nonresponse of the ventricle to that particular impulse, but by the presence or absence of its effect on subsequent conduction."

Concealed conduction in the A-V junction and its influence on subsequent conduction can also be observed in the human heart. The prolongation of the P-R interval after interpolated ventricular premature systoles is the most obvious example of this phenomenon. The retrograde impulse of the ventricular premature systole penetrates into the A-V bundle or A-V node and is stopped before reaching the auricles. The next sinus impulse finds the A-V junction still affected by the retrograde impulse, and this is reflected in the prolonged A-V conduction time of the postextrasystolic beat. Actually, the same mechanism sometimes may be responsible for the complete blocking of the postextrasystolic sinus impulse giving rise to the fully compensatory pause. The region of the A-V junction affected by the retrograde impulse of the ventricular premature systole, rather than the refractory state of the ventricular muscle, may be responsible for the failure of the postextrasystolic sinus impulse to elicit a ventricular response.

Lewis and Oppenheimer⁷ demonstrated, in the experimental animal, increase in the grade of partial A-V block following ventricular premature systoles in the absence of retrograde auricular stimulation. Rothberger⁸ pointed out that ventricular premature systoles occurring in the presence of auricular fibrillation, particularly bigeminal rhythm after administration of digitalis, tend to be followed by a ventricular pause which is longer than the average interval between two transmitted beats. This can only be explained by inhibition of the A-V conduction by the impulse of the ventricular premature systole, which penetrates in a retrograde fashion into the A-V junction.

In the unusual cases of complete A-V block with retrograde response, it can be demonstrated (Winternitz and Langendorf⁹) that the blocked forward impulses penetrate into the A-V junction and influence the retrograde conduction of the idioventricular beats; only those idioventricular beats which occur in late auricular diastole are followed by retrograde P waves, and the retrograde conduction times vary inversely with the preceding P-R distance. The effect of a blocked impulse on the succeeding conducted impulse is also evident in the unique case of 2:1 A-V block with reciprocal auricular beats, reported by Wolferth and McMillan.¹⁰ Here, the P-R interval of the beat following a blocked sinus impulse is longer than the P-R of the beat following an impulse that was conducted to the auricles in a retrograde fashion. This can be explained by the fact that the period of rest in

the depressed region of the A-V junction is greater when a forward impulse follows a conducted retrograde impulse than when two forward impulses occur in succession, the first of which must have entered the region of block without traversing it. A similar mechanism was assumed by Wolferth¹¹ to explain an arrhythmia suggesting a supernormal recovery phase. A retrograde impulse which penetrates into the region of A-V block may prevent a simultaneous sinus impulse from penetrating into the same region a little later; thus, the rest period of the critical area is prolonged and this may allow complete conduction of the subsequent sinus impulse.

However, it is conceivable that the effect of blocked impulses upon subsequent conduction may manifest itself not by inhibition but by enhancement, since the existence of a supernormal phase of conduction in damaged tissue has been demonstrated.¹² This may apply to forward conduction following blocked retrograde impulses or to retrograde conduction following blocked forward impulses. Such an explanation was actually offered¹³ to account for the occurrence of retrograde conduction in a case of complete A-V block.

Lewis and Master⁵ showed that a blocked A-V impulse may not only delay the transmission of the subsequent impulse but may prevent it from reaching the ventricles, so that multiple blockage takes place. Wenckebach and Winterberg¹⁴ considered it likely that the multiple blockage associated with auricular flutter is also an incomplete one in the sense that only the last of the blocked flutter impulses is blocked completely, whereas the others penetrate into the junctional tissues and are stopped before reaching the ventricle. They suggested that such invisible and varying inhibitory effects of the blocked flutter impulses may account for the difficulty, if not impossibility, of analyzing some curves of auricular flutter with a varying ratio of A-V conduction. Kaufmann and Rothberger¹⁵ reported a case of auricular flutter with 2:1 conduction and alternans of A-V conduction. They explained the phenomenon by assuming that the alternate blocked flutter impulse penetrates into a limited portion of the junctional tissues; the varying and alternating conduction times of the conducted impulses can readily be accounted for by the varying distance affected by the alternate blocked impulse, as will be shown in one of our own observations.

Recently, we observed¹⁶ a most unusual case presenting the effect of blocked A-V nodal impulses on subsequent conduction. In a record with frequent nodal premature systoles, there were instances of "dropped beats" without preceding lengthening of P-R, and in one instance, a sudden P-R prolongation of a single sinus beat. Careful analysis of the record revealed that the "dropped beats" were due to interference in the A-V junction of the sinus impulse with the retrograde impulse of a blocked nodal premature systole, and the unexplained P-R prolongation of a single sinus beat was due to a blocked and interpolated nodal premature systole.

Concealed response in the A-V junctional tissues does not only influence subsequent impulse conduction; it may also have an effect on the formation of impulses. In A-V dissociation, where the ventricles are under the control of an A-V nodal pacemaker while the auricles are under the control of the slower S-A node, the sinus impulses occurring at an opportune time are conducted to the ven-

tricles and give rise to early ventricular responses, ventricular capture. These conducted sinus impulses pass through the region of the A-V nodal pacemaker and discharge it, so that the time schedule of the nodal pacemaker is disturbed and its impulse formation starts anew. Instances have been reported¹⁷⁻²³ indicating that under the preceding circumstances the sinus impulse may pass the region of the A-V nodal pacemaker but not reach the ventricles. The blocked sinus impulse penetrates into the A-V junction and before fading out destroys the immature A-V nodal impulse, thus postponing the nodal discharge and causing a disturbance of the ventricular rhythm.

The following four examples are reported to further demonstrate the effect of blocked impulses. Fig. 1 shows a phenomenon which has been observed

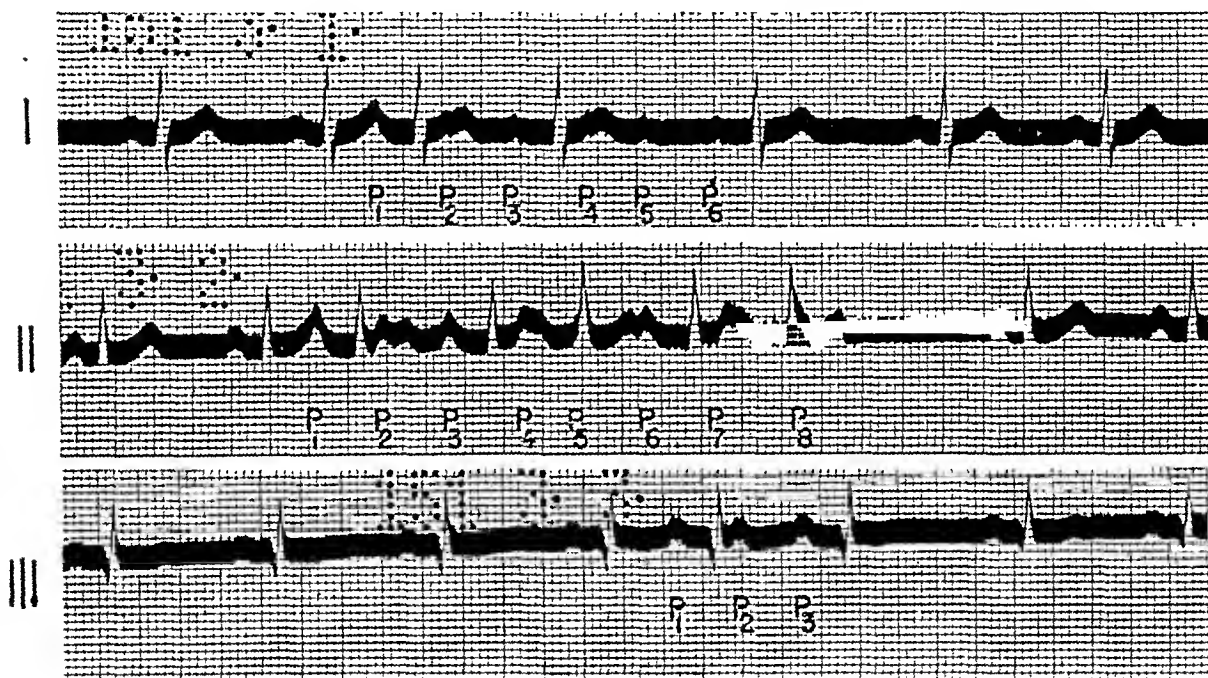


Fig. 1.—Record obtained on a 64-year-old man without signs of cardiac failure. In Lead I, two sinus beats are followed by a run of six auricular premature systoles (P_1 - P_6), of which the first, third, and sixth are conducted, whereas the second, fourth, and fifth are not followed by a ventricular complex. P_1 appears on top of T of the second sinus beat and is conducted with a P-R interval of 0.24 second. While P_2 , with an R-P of 0.12 second, is blocked, P_4 , with a slightly longer R-P (0.13 second), is not only blocked but is followed by another blocked P (P_5). Note that impulse P_5 is blocked, although it occurs much later in diastole than P_1 which was conducted. Impulse P_4 must have penetrated into the junctional tissues and made them refractory when the subsequent impulse (P_5) arrived; this assumption is substantiated by the findings in Lead II. The fact that P-R of the third premature beat is 0.02 second longer than that of the sixth premature beat suggests that the blocked impulse P_2 also affected the A-V junction. In Lead II, after two sinus beats, a run of eight auricular premature systoles (P_1 - P_8) occur in succession, the first, third, fourth, sixth, and seventh are followed by a ventricular complex, the second, fifth, and eighth are blocked. Of the conducted ones, P_4 and P_7 occur rather early in diastole, having an R-P of 0.16 second and 0.15 second, respectively. The blocked impulses occur after an R-P of 0.10 second (P_2), 0.03 second (P_5), and 0.03 second (P_8); in this lead the blocked impulses have no demonstrable effect on the P-R of the subsequent beat. In Lead III, after four sinus beats, three premature P waves (P_1 - P_3) occur in succession. The middle one, with an R-P of 0.115 second, is blocked but affects the transmission time of the succeeding premature auricular impulse (P_3), which measures 0.24 second as compared with 0.21 second of the preceding one (P_1); the difference of 0.03 second is very significant, considering the fact that P_3 occurs later in diastole than P_1 . This case presents a "phase of interference" which follows the actual absolute refractory phase and precedes the period during which impulses are followed by a ventricular response. The short strips do not allow an accurate determination of the duration of the phase of interference. It begins, at most, 0.115 second after the start of QRS and it ends at least 0.13 second after QRS, thus lasting for at least 0.015 second.

before.^{14,24} When two auricular premature systoles occur in succession, the first of which is "blocked," the blocked auricular impulse may give rise to undue prolongation of the P-R of the subsequent auricular premature systole or may actually be responsible for a failure of the ventricles to respond to the second premature impulse, so that two blocked auricular premature systoles occur in succession.

Fig. 2 shows a second degree A-V block varying between 2:1, 3:2, and 4:2. All ventricular beats in Leads I and II are considered to be conducted, since Lead III shows a ventricular pause which is considerably longer than any pause in Leads I or II. Some of the conducted P waves occurring late in ventricular diastole are transmitted with a P-R shorter than that of other beats occurring earlier in diastole (compare P_3 - R_3 of Cycle 3 with that of Cycle 4 in Lead I). This can be explained by the effect on subsequent conduction of a blocked impulse belonging to the P wave partly hidden in the preceding QRS complex. The assumption that such early auricular impulses actually penetrate into the A-V junction without reaching the ventricles is substantiated by the occurrence in the same record of a ventricular response to impulses falling only 0.01 second later in the ventricular cycle (namely, Lead II, Cycle 4). On one occasion such a blocked but almost conducted impulse not only postponed the transmission of the succeeding impulse but actually prevented it, so that a double blockage occurred (namely, Lead III, Cycle 6). The disturbance of impulse conduction observed in this patient is analogous to that produced by Lewis and Master⁵ in the dog's heart by "shifting the middle (blocked) auricular beat" in 2:1 A-V block, so that the middle P occupies a different position in the cycle, preceding, falling into, or occurring after the "phase of interference." Tables I and II demonstrate the effect of the blocked impulses (P_2) on the transmission time (P_3 - R_3) of the subsequent impulses (P_3). It can be seen that this effect is dependent on the duration of R_1 - P_2 which indicates the time at which the impulse of P_2 falls in the cardiac cycle. With R_1 - P_2 measuring 0.06 to 0.15 second, P_3 - R_3 measures 0.39 to 0.41 second; with R_1 - P_2 measuring 0.16 second, P_3 - R_3 increases abruptly to 0.46 to 0.48 second; and with R_1 - P_2 measuring 0.17 second or more, P_2 is followed by R_2 (with one exception which will be discussed) and P_3 - R_3 rises to infinity, the auricular impulse (P_3) failing to reach the ventricles. On one occasion (Lead III, Cycle 6), with a R_1 - P_2 of 0.18 second, block occurs for two P waves (P_2 and P_3) in succession. P_1 - R_1 of Cycle 7 is short (0.40 second), indicating that it was not influenced by the preceding impulse (P_3 of Cycle 6) although the latter occurred very late in the cycle; this in turn proves that the impulse P_2 of Cycle 6 was responsible for the blockage of P_3 of this cycle. In this instance, the delaying effect of a blocked impulse is so great as to equal that of a conducted one, thus causing actual blockage of the subsequent impulse.

Fig. 3 is similar to the case of Kaufmann and Rothberger¹⁵ mentioned previously; it shows a case of auricular flutter with 2:1 A-V conduction and an alternans in the spacing of R-R. The diagram of Lead I, Fig. 2, which applies to the same mechanism in a case of sinus rhythm with 2:1 A-V block, illustrates how such pseudoalternans of the A-V conduction can be explained by the effect of the

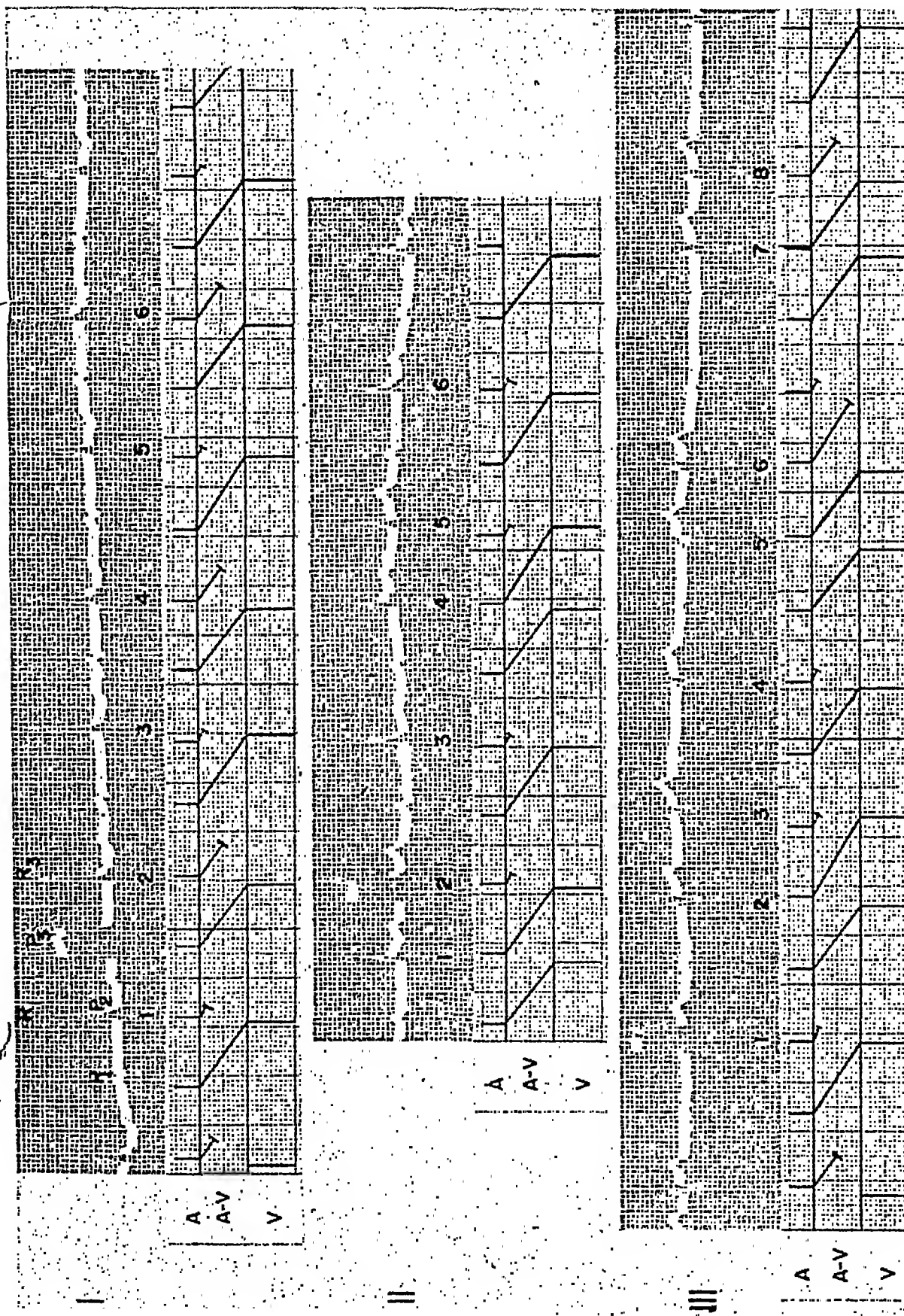


Fig. 2.—This record was taken on a 53-year-old man with subacute bacterial endocarditis superimposed on an old endocarditis of the rheumatic type involving the aortic valve. Autopsy, performed three days after this record was taken, revealed an erosive mycotic aneurysm involving both the interatrial and interventricular septa. The mechanism of the conduction disturbance is illustrated in the diagram below the electrocardiogram. The conventions are those used customarily. A-V represents the spread of the impulse through the A-V junction between the auricles (A) and the ventricles (V). Blockage of an impulse is indicated by short lines at right angles to the oblique lines representing the impulse spread; varying length of the oblique lines representing blocked impulses indicates the varying distance to which the blocked impulses penetrate into the A-V junction. The numerals beneath the QRS represent the beginning of the cycles of beats referred to. In Lead I the P waves and R waves pertaining to a cycle are labelled P₁, P₂, P₃, R₁, and R₂, respectively. Discussed in text.

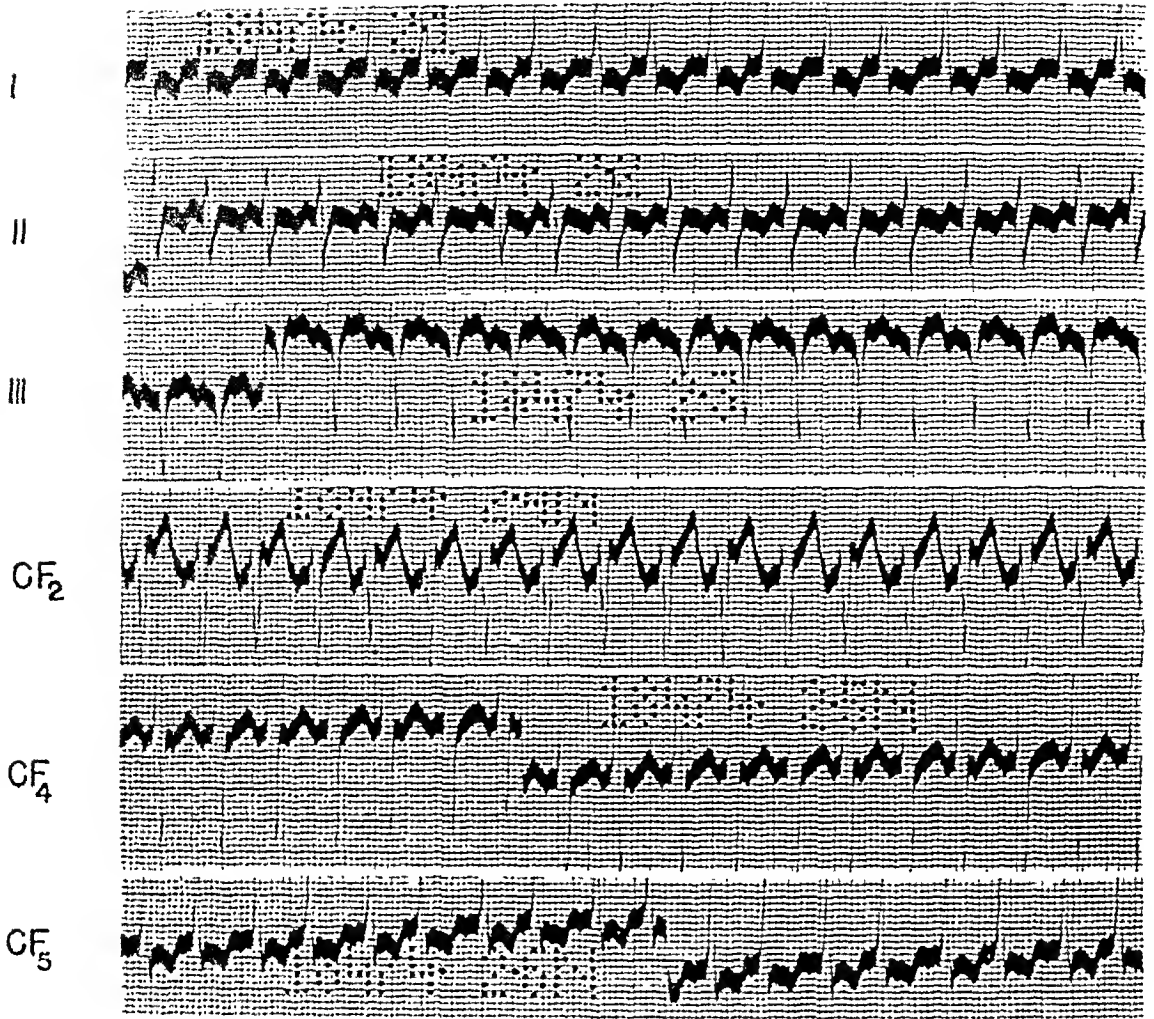


Fig. 3.—Auricular flutter with 2:1 A-V conduction. The flutter waves occurring at a rate of 316 per minute are clearly seen in Leads II, III, CF_2 , and CF_4 . The ventricular rate shows a regular irregularity, in that a long R-R alternates with a short R-R, the difference measuring 0.03 to 0.04 second; this is easily recognized by comparing the intervals between the R waves and the preceding F waves, or the intervals between the R waves and the subsequent F waves. The alternation in contour of the ventricular complexes can be accounted for in part by different superimposition of QRS-T and the F wave. The alternation in length of the F-R intervals of the conducted flutter impulses can be explained by the alternating effect of the blocked flutter impulses (compare with the identical mechanism in Fig. 2, Lead I).

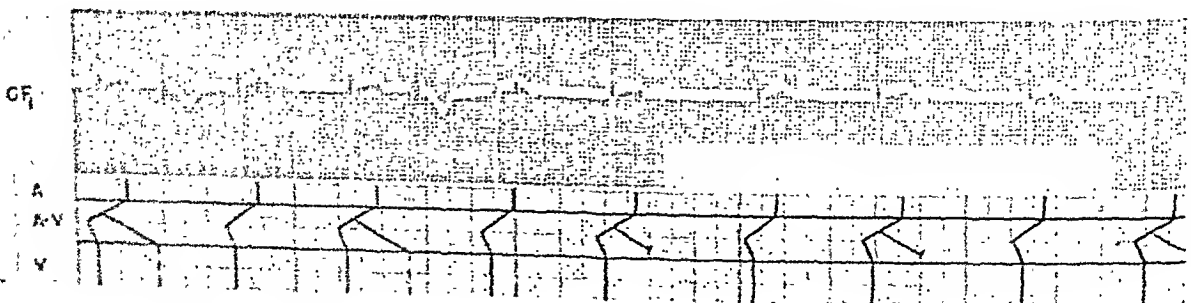


Fig. 4.—Conventions as in Fig. 2. The reciprocal beats showing aberrant ventricular conduction are represented by dashed lines. Discussed in text.

alternate blocked auricular impulse which penetrates into the junctional tissue. It cannot be determined whether all blocked flutter waves fall in the "phase of interference," with the one occurring later in the cycle exerting the more marked

TABLE I. MEASUREMENTS OF THE RECORD ILLUSTRATED IN FIG. 3*

LEAD	CYCLE	P ₁ -R ₁	R ₁ -P ₂	P ₂ -R ₂	P ₂ -P ₃	P ₃ -R ₃	R ₁ -P ₃
I	1	44	13	∞	56	40	69
	2	40	16	∞	57	48	73
	3	48	6	∞	56	40	62
	4	40	16	∞	57	48	73
	5	48	10	∞	56	40	66
	6	40	16	∞	56	46	72.5
II	1	38.5	18	44	56	∞	
	2	44	12	∞	56	41	68
	3	41	13.5	∞	58	40	71.5
	4	40	17	50	60	∞	
	5	50	6	∞	56	41	62
	6	41	15	∞	56	40	71
III	1	46	13	∞	56	40	69
	2	40	19	50	58	∞	
	3	50	8	∞	56	41	64
	4	41	15	∞	58	39	73
	5	39	20	44	58	∞	
	6	44	18	∞	60	∞	78
	7	40	19	44	60	∞	
	8	44	16	∞	60	48	74

*The end of P was easier to determine than its beginning; for that reason, in the above figure, P stands for the end of P and R for the beginning of QRS. All measurements are in hundredths of a second. Discussed in text.

TABLE II. MEASUREMENTS OF TABLE I ARRANGED IN ORDER OF INCREASING DURATION OF R₁-P₂ TO DEMONSTRATE THE INFLUENCE OF THE POSITION OF P₂ ON P₃-R₃

R ₁ -P ₂	P ₂ -R ₂	P ₃ -R ₃
6	∞	40
6	∞	41
8	∞	41
10	∞	40
12	∞	41
13	∞	40
13	∞	40
13.5	∞	40
15	∞	40
15	∞	39
16	∞	48
16	∞	48
16	∞	48
16	∞	46
17	50	∞
18	44	∞
18	∞	∞
19	44	∞
19	50	∞
20	44	∞

influence upon subsequent conduction; or whether only those of the blocked flutter impulses which fall late in diastole occur during the "phase of interference," whereas those occurring early in the ventricular cycle fall into the "actual" absolute refractory phase and have no effect on the "F-R" of the succeeding beat.

Fig. 4 shows an example of disturbed impulse formation due to a mechanism which to our knowledge has not been reported before. The patient on whom the record was obtained was a 76-year-old woman with arteriosclerotic heart disease and congestive heart failure who developed the illustrated arrhythmia after digitalization. The record (Lead CF₁) shows the whole heart to be under the control of the A-V node; all nodal beats are followed by a retrograde P wave. The retrograde contour of P was clearly evident by comparing the P wave pattern in the limb leads with that observed at the time of sinus rhythm. The retrograde conduction times in Fig. 4 alternate in length, measuring 0.28 second and 0.20 second; the R-R distances between the nodal beats also alternate in length, measuring 1.26 to 1.31 seconds and 1.00 to 1.05 seconds. The explanation for the latter phenomenon is given by the first portion of the record which shows on two occasions another ventricular complex following the longer retrograde conduction. This beat represents a reciprocal beat with aberrant ventricular conduction, and the long ventricular pauses in the second portion of the record are due to the occurrence of blocked reciprocal beats. The reciprocal impulse passes the nodal pacemaker, but is blocked below it before reaching the ventricles. The premature discharge of the nodal pacemaker is responsible for the lengthening of the alternate R-R intervals. The R-R intervals containing a reciprocal beat are almost identical in duration with the long R-R intervals without a reciprocal beat, the latter actually containing a blocked reciprocal beat. For the sake of simplicity, it is assumed in the diagram to Fig. 4 that the time for forward conduction of the A-V nodal beats remains constant; actually, it may be slowed after the transmission of a reciprocal beat^{25,26} with the consequence that (a) the apparent improvement of the retrograde conduction time in the beat following a reciprocal impulse may partly be due to a delay in forward conduction, and (b) the cycle length of the A-V nodal pacemaker may be longer than the short R-R interval of two successive nodal beats seems to indicate.

SUMMARY AND CONCLUSIONS

1. The spread of an impulse which affects the A-V junction by penetrating into it without traversing it, thus failing to reach the auricles or ventricles (depending on the direction in which the impulse travels), finds no direct expression in the electrocardiogram. Indirect evidence for such concealed A-V conduction is the influence of the blocked impulse on the transmission time or on the formation of a subsequent impulse.

2. The literature dealing with the effect of blocked impulses on conduction and formation of subsequent impulses is reviewed.

- (a) The simplest example of the effect of a blocked impulse is the post-extrasystolic P-R prolongation due to blocked retrograde conduction after an interpolated ventricular premature systole.

(b) Similarly, the failure of the sinus impulse following a ventricular premature systole to elicit a ventricular response may be due, in some instances, to the inability of the A-V junctional tissues to transmit the impulse after it has been affected by the blocked retrograde impulse of the ventricular premature systole, and not to refractoriness of the ventricular muscle.

(c) The pause after ventricular premature systoles in the presence of auricular fibrillation indicates that a retrograde impulse has affected the junctional tissues.

(d) The increase in the grade of a partial A-V block following ventricular premature systoles, even if they are not followed by a retrograde P, demonstrates the effect of blocked retrograde impulses.

(e) Cases of complete forward block in the A-V junction and preserved retrograde response show the effect of the blocked forward impulse on subsequent retrograde conduction.

(f) A blocked retrograde impulse, by reaching a depressed area in the A-V junction prematurely, may prolong the period of rest in that area and thus shorten the conduction time of the subsequent forward impulse.

(g) It is conceivable that, in depressed cardiac muscle, an impulse falling into the supernormal phase of a preceding blocked impulse may be conducted faster instead of being delayed by the effect of the blocked impulse.

(h) Multiple blockage may occur as a result of a blocked impulse which was partially conducted and which influenced the subsequent impulse in the same way as a completely conducted one; such a mechanism is probably common in auricular flutter.

(i) A blocked A-V nodal premature systole may account for a "dropped beat," and a blocked and interpolated nodal premature systole can give rise to an apparently unexplained P-R prolongation of a single beat.

(j) In cases of A-V dissociation, some of the impulses of the slower pacemaker (S-A node), after passing and discharging the faster A-V nodal pacemaker, may be stopped below the latter before reaching the ventricles. The result of such concealed A-V conduction is a disturbance in the impulse formation of the nodal pacemaker.

3. Three new instances demonstrating the effect of blocked A-V impulses on succeeding impulse conduction and one showing the influence on subsequent impulse formation are reported and illustrated. They demonstrate: (a) the effect of a blocked auricular premature systole on A-V conduction of a subsequent auricular premature systole from the same focus; (b) the effect of the blocked auricular impulses on subsequent A-V conduction in a case of 2:1 A-V block, depending on the exact position of the blocked P wave in the cardiac cycle, and confirm the existence of a "phase of interference" and explain the transition from one grade of block to another; (c) the effect of the blocked flutter impulses in a case of auricular flutter with 2:1 A-V conduction giving rise to a pseudo-alternans of A-V conduction; and (d) a hitherto unreported disturbance of impulse formation, namely, discharge of the A-V nodal pacemaker by blocked reciprocal beats.

4. These observations support the view that concealed A-V conduction may account for the difficulty in analyzing some curves of auricular flutter with a varying ratio of A-V conduction. The same phenomenon may also explain some of the discrepancies encountered in the construction of recovery curves of A-V conduction in cases of partial A-V block based on simple correlation of P-R and R-P.

The author is indebted to Dr. L. N. Katz for his valuable criticism.

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THE BEHAVIOR OF THE VENOUS PRESSURE DURING VARIOUS STAGES OF CHRONIC CONGESTIVE HEART FAILURE

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THE explanation of the pathologic physiology of congestive heart failure is today, as ever, a perplexing problem in medicine. Opinion has shifted from one theory to another as various investigators have brought forth additional data and propounded new ideas. The two basic explanations have been termed the forward failure theory and the backward failure-theory of chronic congestive heart failure. The former may briefly be stated as follows: the pathology causing the clinical picture of congestive heart failure occurs in the organs supplied by the failing chambers of the heart and is due to a decrease in the blood flow through these organs. The latter theory holds that the pathology leading to the clinical picture of congestive heart failure occurs in the tissues feeding blood to the failing (enlarged) chambers of the heart, the essential phenomenon being an increase in the intracapillary pressure in these tissues.

Although the principles of the backward failure theory were well enumerated over one hundred years ago,¹ it did not become generally accepted until the last decade when it was again brought to attention.² In the interim, the majority of observers were advocates of the forward failure theory,³⁻⁶ and as recently as 1933 it was the more widely accepted of the two theories.⁷ For the past several years the backward failure theory has been generally accepted, but more recent investigations have brought forth data which are difficult to explain in the light of this theory. These data include (1) the absence of edema in the lower extremities after ligation of the inferior vena cava, despite extremely high venous pressures in these limbs,⁸ (2) the failure of the venous pressure to show a rise after severe damage to the right ventricle in dogs,⁹ and (3) the finding of a gain in weight and an increase in plasma volume before the venous pressure reaches abnormal levels following administration of salt to compensated cardiac patients.¹⁰ These and other facts which are difficult to explain by either the forward or backward failure theory have been discussed.¹¹ Other possible explanations involving sodium metabolism¹²⁻¹⁴ and the role of the kidney^{10,11} in congestive heart failure have been suggested, as well as the action of hormones¹⁵ involving either the kidney¹⁶ or the liver¹⁷ and sodium metabolism.

This study was undertaken because of the lack of adequate data showing the day-to-day behavior of the venous pressure in congestive heart failure, and

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to ascertain, as accurately as possible, the relation of the venous pressure to the state of the congestive heart failure.

METHODS AND MATERIALS

Patients.—Twenty-three Negro patients who entered the hospital in congestive heart failure (all in Functional Class IV) were observed. Of these, eight were women and fifteen, men. Their ages varied from 19 to 66 years. The causes of their heart disease were: hypertension, 13 patients; syphilis, 6; senile arteriosclerosis, 3; and rheumatic fever, 1 patient. No attempt was made to influence the therapy. The regular hospital regimen for congestive heart failure was employed in all patients. Two of the patients died while being studied, one (Number 2) of a coronary occlusion and the other (Number 20) of uremia due to an associated chronic glomerulonephritis. Multiple episodes of decompensation and recovery were observed in four patients (Numbers 7, 8, 9, and 12) during their hospital stay. On three occasions, decompensation was brought about by the administration of 12 Gm. of sodium chloride per day. A total of thirty-four significant changes in the state of congestive heart failure, as evidenced by weight gain or loss, were observed. Pertinent data concerning the patients are summarized in Table I.

TABLE I. PERTINENT DATA ON PATIENTS STUDIED

SUBJECT NUMBER	SEX	AGE	DIAGNOSIS*	DURATION OF HEART DISEASE	NUMBER OF EPISODES OF CHF	TIME SINCE LAST FAILURE	TREATMENT RECEIVED†
1	F	50	HCVD	12 yr.	2	6 mo.	1, 2, 3, 4
2	F	50	LHD	9 mo.	1		1
3	M	42	HCVD	2 mo.	1		1, 2
4	M	53	HCVD	1 wk.	1		1, 2
5	F	51	ASHD	3 mo.	1		1, 2
6	M	29	HCVD	3 wk.	1		1, 4
7	M	62	ASHD	2 mo.	1		1, 3
8	M	46	LHD	14 mo.	2	9 mo.	1, 2, 3
9	F	35	HCVD	2 yr.	3	3 mo.	1, 2, 3, 4
10	M	66	LHD	2 mo.	1		1
11	M	60	ASHD	5 yr.	9	6 mo.	1, 3
12	M	59	LHD	3 mo.	1		1, 2, 3, 4
13	M	49	LHD	2 yr.	1		1, 2, 3
14	M	55	HCVD	2 yr.	2	2 yr.	1
15	F	48	LHD	5 wk.	1		1, 2, 3, 4
16	M	43	HCVD	2 mo.	1		1, 3
17	M	40	HCVD	6 wk.	1		1, 3
18	M	56	HCVD	3 wk.	1		1, 3
19	M	19	RhHD	6 yr.	11	6 mo.	1, 2
20	F	52	HCVD	2 wk.	1		1
21	M	52	HCVD		1		1, 2
22	F	54	HCVD	2 mo.	1		1, 3
23	F	47	HCVD	4 yr.	4	3 mo.	1, 2, 3

*HCVD—Hypertensive cardiovascular disease

LHD—Syphilitic heart disease

ASHD—Arteriosclerotic heart disease

RhHD—Rheumatic heart disease

†1—Low sodium diet (1.6 Gm. NaCl/day) with fluids ad lib

2—Dietalia

3—Mercurial diuretic

4—Ammonium chloride

Venous Pressure.—Serial determinations of the venous pressure demanding daily venepunctures for as long as two months in some cases were made feasible by the Phlebomanometer, a method of direct measurement of venous pressure.¹⁸ This method has been described in the literature¹⁶ but will be briefly discussed. The normal range for the venous pressure in the antecubital vein by this method is 50 to 140 mm. H₂O; the normal variations for other veins have been presented elsewhere.¹⁸ The heart level or reference point, termed the phlebostatic level, is a horizontal plane passing through the phlebostatic axis. This axis is defined as the intersection of a frontal plane lying midway between the anterior and posterior surfaces of the thorax, measured at the xiphisternal junction, and a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. Indelible crosses were made on both sides of the thorax marking the phlebostatic axis so as to achieve a constant reference level for serial determinations. The patient was placed in the same position each day during the study. A carpenter's level on a long rod was employed to insure the position of the vein at the phlebostatic level. Since this method depends on an equalization of pressures¹⁸ rather than on a flow of fluid^{20,21} to achieve equilibrium, the needle used may be of small diameter (No. 22 and No. 24 gauge). The venous pressure in several superficial veins was determined each day on all patients to serve as a check on the values obtained, as well as to show the behavior of the venous pressure in the various parts of the body during various stages of congestive heart failure. All of the precautions previously described¹⁸ were heeded. The range of error of this method as employed was ± 5 mm. of water.

The procedure involved the following: (1) The phlebostatic axis was determined. (2) The vein to be used was placed at the phlebostatic level. (3) Two per cent citrate was drawn into the needle and adaptor so that the fluid level was visible. (4) The needle was inserted into the vein and its pressure quickly equalized by compression of the rubber bulb of the phlebomanometer. Equalization of pressures resulted in a fluid level which was motionless except for the oscillations of venous pulse with respiration. To keep the fluid level constant, the pressure in the rubber bulb was gradually decreased since the venous pressure dropped about 20 mm. H₂O in the first three to four minutes following venepuncture. (5) Four minutes after insertion of the needle, the venous pressure was read from the scale of the manometer. (6) The position of the vein was rechecked with the carpenter's level.

Weight.—Weight was selected as the most accurate practical index of the fluid content of the body. As such, it was considered a good criterion of the state of the congestive failure. The graphs presented, therefore, show the chronological relation of the changes in weight to the alterations in venous pressure as the patient improved or became more decompensated.

A platform type scale was used which was accurate to one-fourth pound. The patients were weighed daily at 10:00 A.M. to give a constant relation to meals and, in so far as possible, to bowel function. The patients were asked to void just prior to being weighed and only the hospital gown was worn. The initial

position of the lever arm was checked before each weighing and two determinations of each weight were taken.

The majority of the initial studies on the patients recovering from congestive heart failure were done at the time of admission to the wards and all were begun within twelve hours after entering the hospital. None had received specific therapy prior to the initial determinations of weight and venous pressure. The patients who showed a change for the worse had all been under observation (daily weight and venous pressure) prior to the reversal. The venous pressures graphed represent values obtained daily in the antecubital vein, although pressures in multiple veins were taken each day. The antecubital vein was chosen because it is technically the best suited for the purpose, being large and superficial. In addition, the chance of error due to spasm of this vein is minimal, and the antecubital space is least painful of all areas presenting a superficial vein for venepuncture. Any change in venous pressure or weight exceeding the range of error for the methods employed was considered an actual change. Because the relative importance of small variations in weight and venous pressure could not be evaluated, the rates at which the total changes in weight and venous pressure were achieved were determined by the method that will be described.

RESULTS

Significant changes in the degree of congestive heart failure were encountered thirty-four times. The chronological relationship of the rise or fall in venous pressure to the change in weight was noted (Table II, *A*). These data were further divided, depending on whether or not the patient was becoming more or less congested (Table II, *B*).

TABLE II. RELATIONSHIPS OF CHANGE IN VENOUS PRESSURE TO CHANGE IN BODY WEIGHT

A. Chronological Relationship of Venous Pressure to Weight in Thirty-four Instances of Change of State of Congestive Heart Failure		
1. Simultaneous change in weight and venous pressure		20 (59%)
2. Venous pressure change preceding the change in weight		8 (24%)
3. Weight change preceding the change in venous pressure		6 (17%)
B. Chronological Relationship of Venous Pressure to Weight in Twenty-six Patients Recovering from Congestive Heart Failure and in Eight Patients Decompensating		
1. <i>Recovering</i>		
Group 1. Simultaneous weight and venous pressure decrease		16 (62%)
Group 2. Venous pressure decrease preceding drop in weight		6 (23%)
Group 3. Weight drop preceding decrease in venous pressure		4 (15%)
2. <i>Decompensating</i>		
Group 4. Simultaneous weight and venous pressure increase		4 (50%)
Group 5. Venous pressure increase preceding weight increase		2 (25%)
Group 6. Weight increase preceding venous pressure rise		2 (25%)

Composite graphs of the daily changes in the weight and venous pressure observed in the patients of the six groups (Table II, B) are given (Figs. 1, 2, 3, 4, 5, and 6). In addition, for each of the thirty-four significant changes in the state of congestion, the total change in venous pressure and weight was noted, as well as the time in days required for each total change to be achieved. The per cent of the total change that was achieved each day was calculated. Composite graphs of these values could not be made directly without distorting the relation of weight to venous pressure since some patients achieved their total change in three days while others required ten days and longer. For this reason, the duration of each significant change was noted and divided into fifths. The per cent of total change achieved during each fifth of total duration of change was computed (small graphs in Figs. 1, 2, 3, 4, 5, and 6).

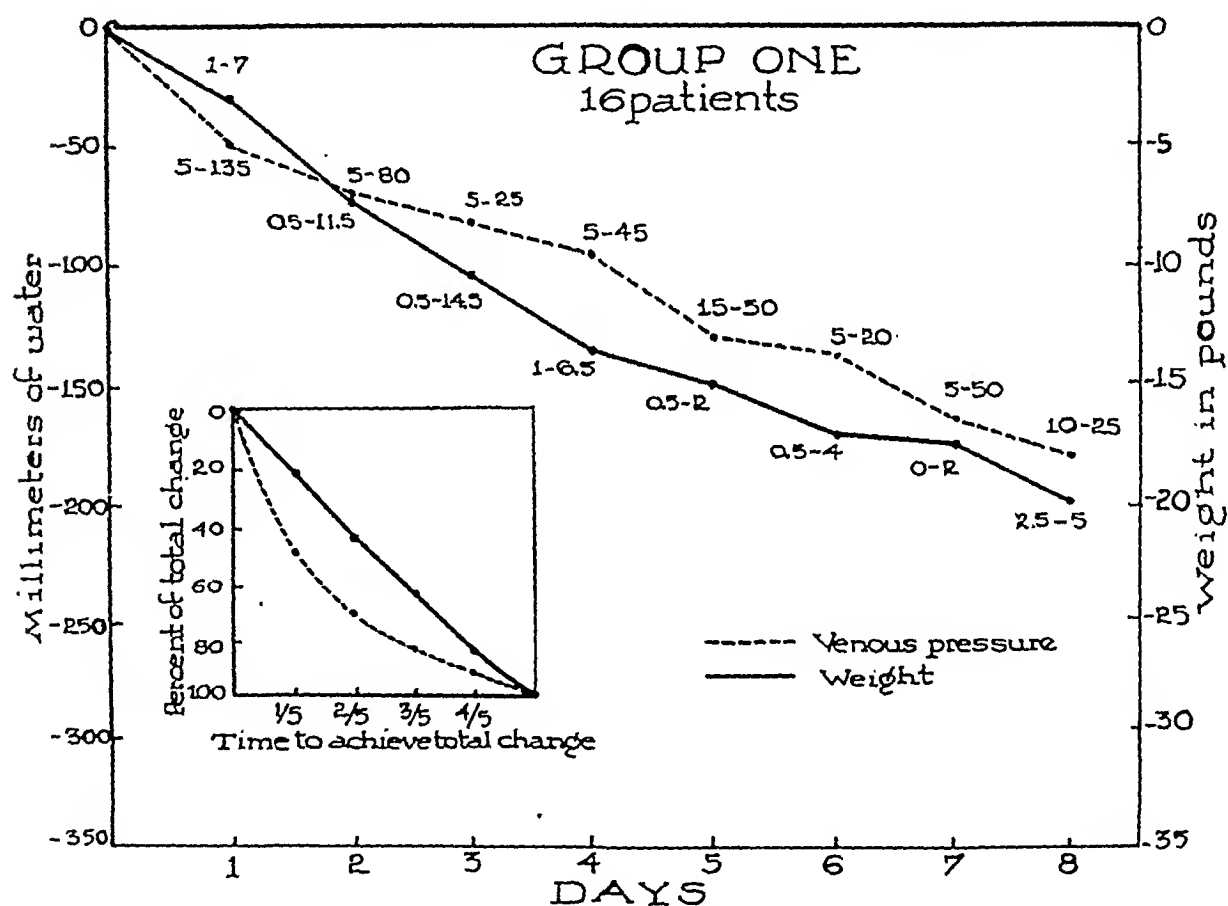


Fig. 1.—A composite graph showing the time relation of changes in venous pressure to weight in sixteen patients recovering from congestive heart failure. There were no independent decreases of weight or venous pressure in these patients. The small graph represents the average per cent of total change in weight and venous pressure that was achieved during each one-fifth of the time necessary to accomplish the total change (see text). In this, and in all graphs to follow, the values indicated near the points (mean values) in the curves are the extremes for the group.

Patients Recovering From Congestive Heart Failure.—Twenty-six instances of recovery from congestive heart failure were observed (Table II, B). In sixteen of these, the weight and venous pressure at the end of the first hospital day had decreased from the values obtained on admission (Fig. 1). The average weight loss over this period was 3.0 pounds (range, 1.0 to 7.0 pounds) and the mean

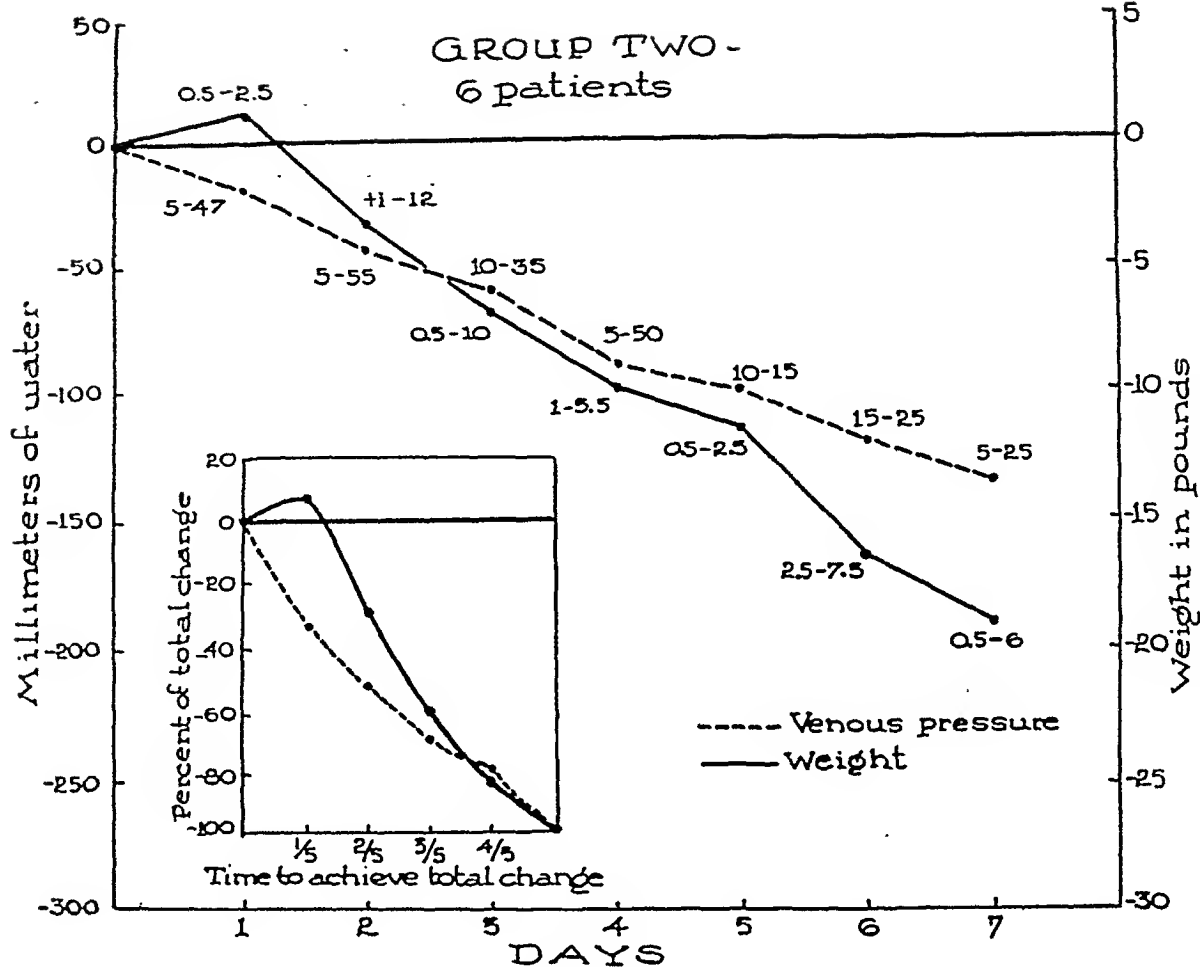


Fig. 2.—A composite graph showing the behavior of venous pressure and weight in six patients recovering from congestive heart failure. In these patients the venous pressure decreased from 5 to 47 mm. H₂O prior to the initial decrease in weight. The small graph shows the per cent of total change achieved during each one-fifth of time of total change. The venous pressure began to fall first, but weight finally fell at a faster rate.

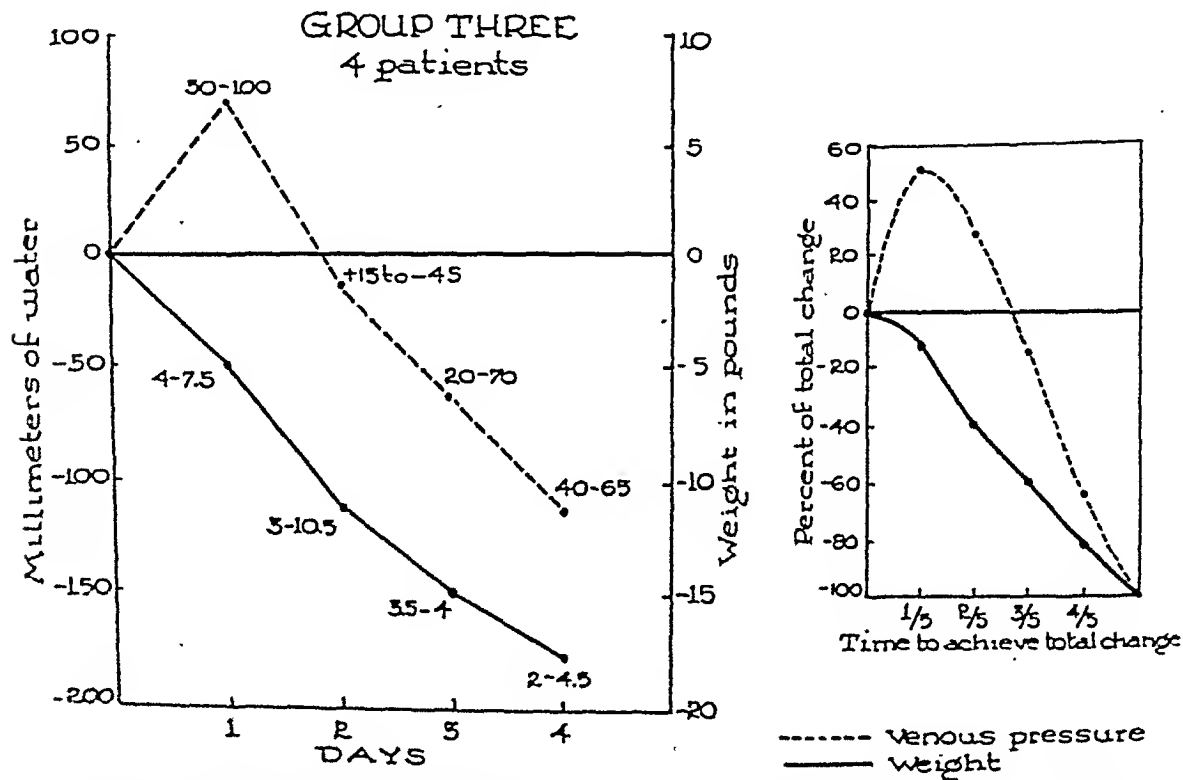


Fig. 3.—A composite graph of four patients recovering from congestive heart failure. The relation of weight loss to venous pressure change is noted. The weight began to fall prior to the venous pressure decrease. The small graph shows the per cent of total change achieved during each one-fifth of time of total change. The weight began decreasing first, but the venous pressure finally fell at a faster rate.

venous pressure decrease was 49 mm. H₂O (extremes, 5 mm. H₂O and 135 mm. H₂O). Although both the venous pressure and weight decreased each day in these sixteen patients (Fig. 1, large graph), the venous pressure achieved its total change at a faster rate initially than did the weight (Fig. 1, small graph).

In six of the twenty-six patients recovering from congestive heart failure, the weight had risen from 0.5 to 2.5 pounds above the initial level after one hospital day (Fig. 2). In this period the venous pressure had dropped 5 to 47 mm. of water. In two patients there was a further increase in weight on the second hospital day despite a continued fall of venous pressure. By the third day, the weight of all six patients had begun to fall but only subsequent to an average decrease in venous pressure of 45 mm. of water. The venous pressure achieved its total decrease at a faster rate initially than did the weight (Fig. 2, small graph).

In four of the twenty-six patients recovering from congestive heart failure, the venous pressure had risen after one hospital day from 50 to 100 mm. H₂O above the initial value (Fig. 3), while the weight had decreased from 4.0 to 7.5 pounds.

Patients Becoming More Congested.—Eight patients were observed as their congestive heart failure became worse (Table II, B, 2). Four of these changes occurred in patients with advanced heart disease who, despite therapy, had not completely recovered from a previous episode of congestive heart failure. Three decompensation trends were brought about by administration of 12 Gm. of sodium chloride per day to patients who were not in congestive heart failure. One patient changed from the compensated to the decompensated state despite therapy which included a low sodium diet.

Of the four patients suffering reversals while recovering from congestive heart failure, two showed a weight gain prior to a venous pressure rise (Fig. 6), one showed a venous pressure rise prior to a weight gain (Fig. 5), and one showed a simultaneous rise in both (Fig. 4).

Of the three patients who were given salt, two showed a simultaneous rise in weight and venous pressure (Fig. 4) and one had a rise in venous pressure prior to a weight gain (Fig. 5). The other patient whose venous pressure was normal when decompensation began showed a simultaneous rise in weight and venous pressure while on a low sodium diet.

Patients Showing Changes in Either Weight or Venous Pressure Prior to a Change in the Other.—The patients in Groups 2, 3, 5, and 6 (Table II, B) underwent changes in their state of failure which were characterized by an initial alteration of either weight or venous pressure, but not of both simultaneously. These independent changes are listed (Table III) and the percentage of the total change in weight or venous pressure which they represent is shown. Comparing Groups 2 and 3, patients recovering from congestive heart failure in whom there was not a simultaneous decrease in weight and venous pressure, we see that there is no significant difference in the percentage of the total venous pressure decrease (Group 2) and the percentage of the total weight fall (Group 3) that were achieved

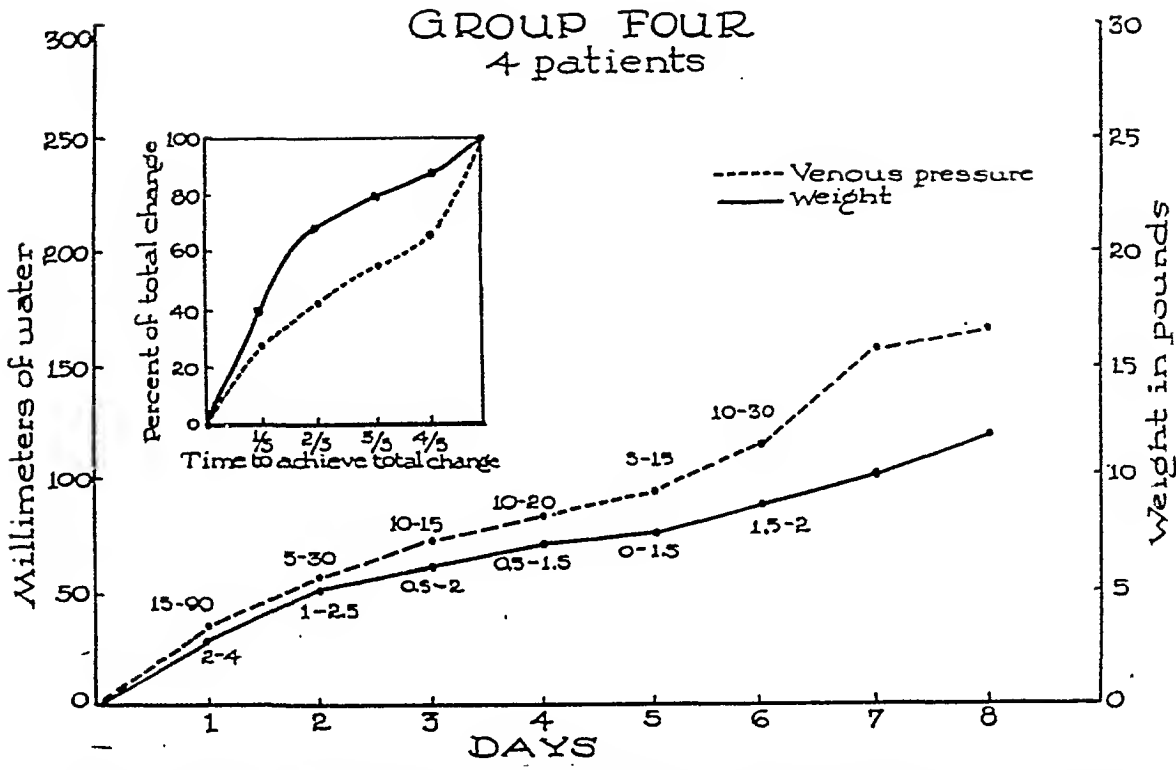


Fig. 4.—A composite graph of four patients developing congestive heart failure. Of these, three had normal venous pressures initially. Two of these three patients received sodium chloride (12 Gm. per day). Both the weight and venous pressure showed a rise each day. The small graph shows the average per cent of total rise in weight and venous pressure achieved during each one-fifth of total duration of the congestive process. Initially, the weight rose faster than the venous pressure; later, the reverse was true.

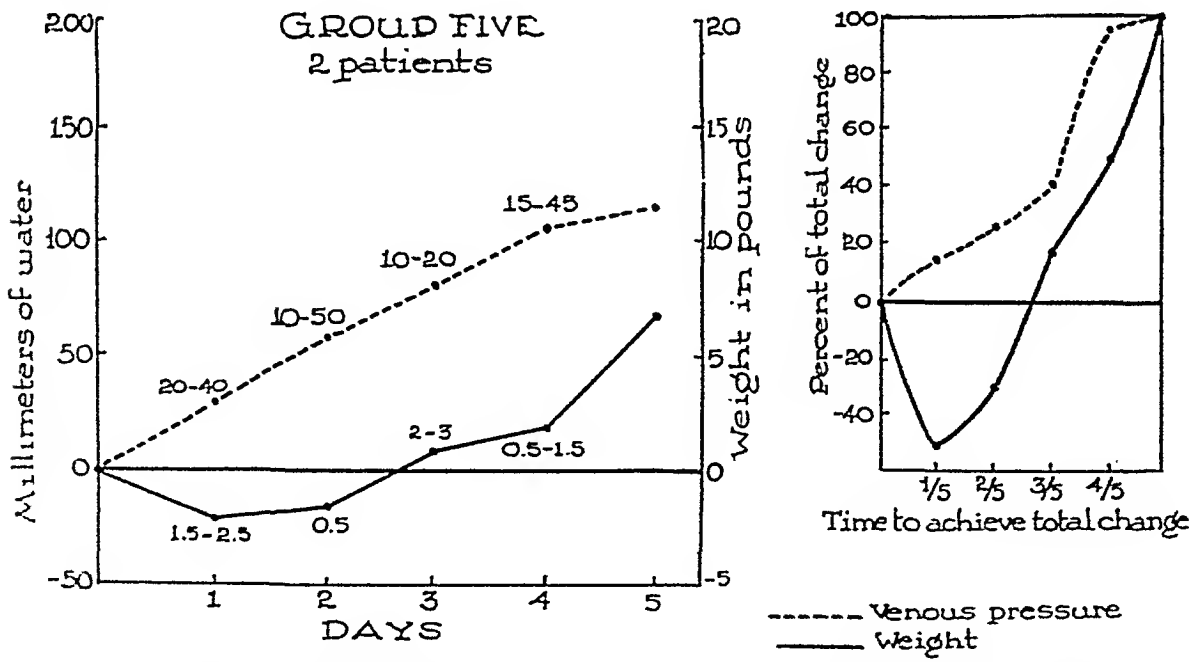


Fig. 5.—The average change in weight and venous pressure for two patients decompensating. One had a normal venous pressure initially and was given 12 Gm. sodium chloride daily. The relation of venous pressure rise to weight gain is shown. The venous pressure rose from 20 to 40 mm. H₂O before the weight began increasing. The small graph represents the per cent of total rise in weight and venous pressure achieved during each one-fifth of the total time of study. The venous pressure began rising although the weight fell. After the weight had achieved 15 per cent of its total rise, the rate of venous pressure rise increased.

independently of the other (compare 44 per cent with 37 per cent). The same may be said of the patients developing more failure (Groups 5 and 6) in whom there was not a simultaneous rise in weight and venous pressure (compare 27 per cent with 22 per cent).

TABLE III. PATIENTS SHOWING A CHANGE IN ONE FACTOR PRIOR TO A CHANGE IN THE OTHER. THE VALUES OF THE INDEPENDENT CHANGES AND THE PER CENT OF THE TOTAL CHANGE WHICH THESE REPRESENT ARE GIVEN

<i>Recovering</i>			
Group 2		Group 3	
1	20 mm. H ₂ O	1	3 lbs.
2	25 mm. H ₂ O	2	7½ lbs.
3	45 mm. H ₂ O	3	4 lbs.
4	60 mm. H ₂ O	4	4½ lbs.
5	25 mm. H ₂ O		
6	25 mm. H ₂ O		
		Avg.	4.9 lbs.
Avg.	33 mm. H ₂ O		
<i>Developing Failure</i>			
Group 5		Group 6	
1	40 mm. H ₂ O	1	2 lbs.
2	20 mm. H ₂ O	2	2 lbs.
Avg.	30 mm. H ₂ O	Avg.	2 lbs.

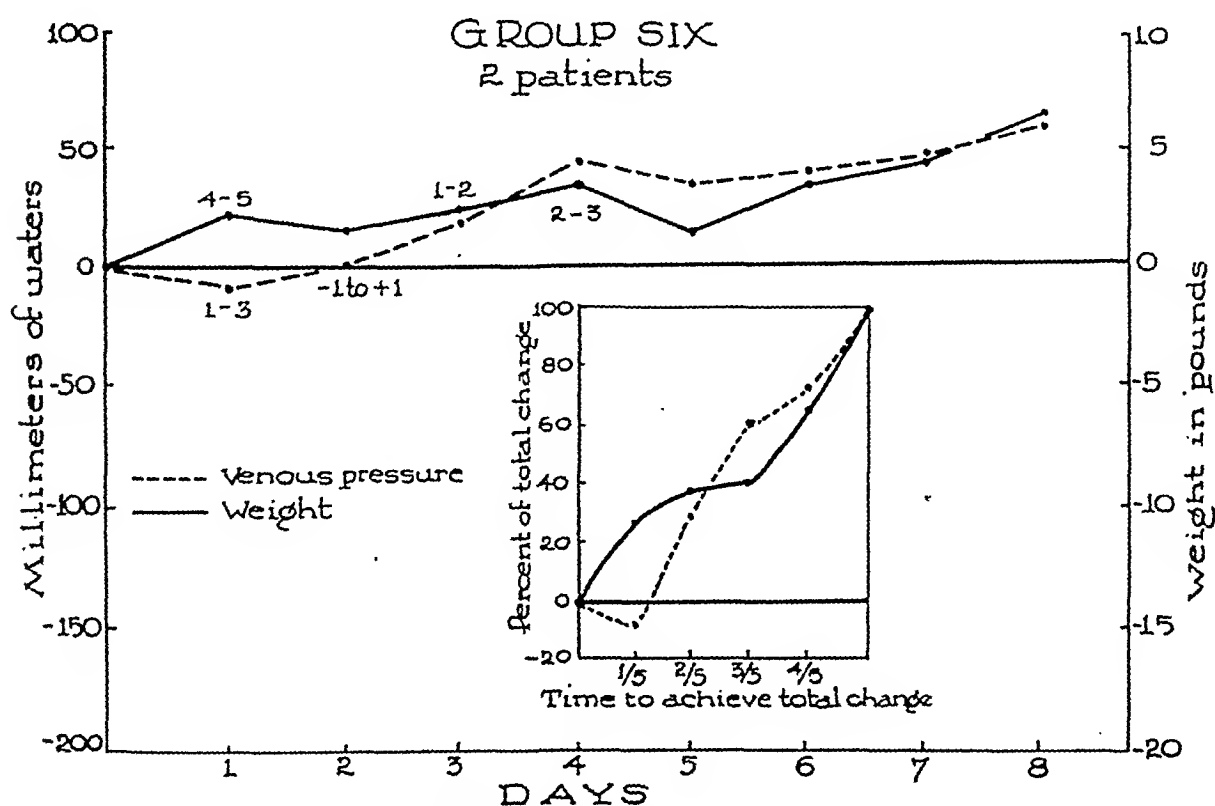


Fig. 6.—The average relation of weight to venous pressure for two patients becoming more severely congested despite treatment. Neither had completely recovered from a recent episode of congestive heart failure when this reversal occurred. Initially, a weight gain preceded the rise in venous pressure. The small graph shows the per cent of total rise in venous pressure and weight achieved during each one-fifth of the congestive process. A rapid rate of venous pressure increase followed the initial rise in weight.

DISCUSSION

In the majority of the patients observed, the behavior of the venous pressure was like that generally reported for patients with cardiac disease.²²⁻³⁰ It was in the normal range when the patients were compensated, rising as the picture of congestive heart failure developed; it was elevated in marked failure, decreasing as recovery progressed, and was normal again when compensation had returned. This confirms the importance of venous pressure determinations in establishing the diagnosis of cardiac decompensation and in evaluating the efficacy of therapy and the progress of the disease. It also indicates the inability to discern impending congestive failure or diminished myocardial reserve in the compensated patient by this procedure.^{29,30}

In some patients admitted in congestive failure, the initial venous pressure was in the normal range despite the presence of signs and symptoms of congestive heart failure. In these patients there was a subsequent decrease in venous pressure as failure disappeared, but all values were in the normal range. This illustrates the value of serial determinations of the venous pressure since some patients may have an elevated venous pressure although the actual value is in the normal range. In other patients, venous pressure on admission was high but dropped rapidly into the normal range, after bed rest alone in some cases, although the weight loss and disappearance of the picture of congestive heart failure occurred gradually over the subsequent few days. Therefore, in such patients, a single venous pressure measurement would be misleading.

Most patients displayed concordant changes in weight and venous pressure, both while recovering or decompensating. This suggests a probable relationship between the two. However, in several patients, either the venous pressure or weight began changing prior to the other. This variable behavior of the venous pressure in congestive heart failure must be explained.

Recent studies have shown that the behavior of the tissue pressure in congestive heart failure is also variable.³¹⁻³⁵ The venous pressure and the tissue pressure are directly inter-related since they are hydrostatic forces on either side of the capillary wall which is freely permeable to water and crystalloids. The behavior of the tissue pressure depends, in part, on the anatomic location of the tissues and their distensibility.³⁶ Therefore, it would seem that the behavior of the venous pressure would depend at least partly on the condition of the tissues as they are subjected to variations in tissue fluid volume. Using the data available in the literature, criteria were drawn up to determine the condition of the tissues in the patients studied. From these (Table IV), the behavior of the venous pressure, that is, the time relation of the initial change in weight to change in venous pressure, was predicted. The predicted behavior agreed with the actual behavior in twenty-seven of the thirty-one cases. Three cases with marked ascites were excluded. These all showed a weight decrease prior to a drop in venous pressure, although when the criteria were applied to these patients it was predicted that their venous pressure and weight should fall concordantly. From this, it seems plausible to assume that the initial weight decrease represented a clearing of the ascites rather than a decrease of edema fluid in the tissues.

The patients who recovered from congestive heart failure with a simultaneous decrease in weight and venous pressure (Group 1) showed initially a faster rate of fall of venous pressure than of weight. This would be expected in view of the relation of the venous pressure to the tissue pressure, as previously discussed. Of the patients showing a simultaneous gain in weight and venous pressure (Group 4), three had recently been in failure. These were expected to show a rise in weight prior to a rise in venous pressure according to the criteria of Table IV. The small graph (Fig. 4) shows that the weight did rise at a faster rate initially than did the venous pressure. The fourth patient had not been in congestive heart failure before. His venous pressure rose at a faster rate than his weight, although this is concealed by the averaging of all four patients (small graph, Fig. 4). These findings are in accord with the hypothesis that the behavior of the venous pressure is affected by the state of the tissues. The relative rates of change in weight and venous pressure in the other four groups may also be explained as a function of the condition of the tissues. The close correlation in these patients of the behavior of the venous pressure with the condition of the tissues is significant. Perhaps the cardiac function has less direct influence on the venous pressure in congestive heart failure than does the state of the tissues. These findings support the work of Starr.³⁷

TABLE IV. CRITERIA FOR EVALUATING THE CONDITION OF THE TISSUES AFFECTED BY CARDIAC EDEMA WITH THE PREDICTED BEHAVIOR OF THE VENOUS PRESSURE FOR EACH CONDITION

CRITERIA	TISSUE	PATIENT	PREDICTED BEHAVIOR OF VENOUS PRESSURE
1 No previous edema 2 No recent edema 3 Moderate edema of short duration	Normal	Recovering Decompensating	Decreases with wt.* loss Increases with wt.* gain
1 Recent edema 2 Frequent previous episodes of edema 3 Marked edema of long duration 4 Edema receding	Easily distensible	Recovering Decompensating	Decreases before wt.* loss Increases after wt.* gain
1 Slight edema present in patient decompensating 2 Fibrotic tissue (scleroderma)	More resistant to distention than normal tissue	Recovering Decompensating	Decreases after wt.* loss Increases before wt.* rise

*Weight change as measurable clinically (scales accurate to one-fourth pound).

From this, it would seem that any implications as to the role of the venous pressure in the production of the syndrome of congestive heart failure which are based on observations on patients recovering from congestive heart failure would not be valid, since the condition of the tissues in decompensation and recovery is different.

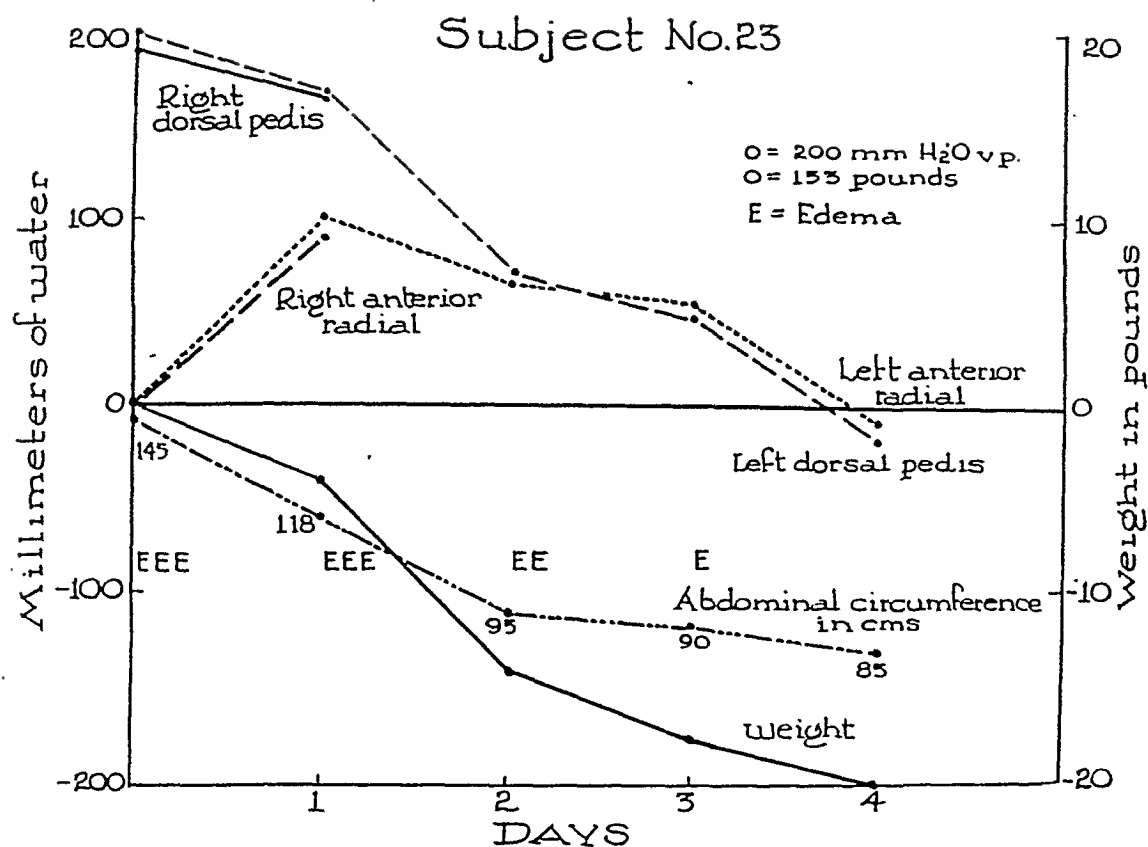


Fig. 7.—A patient with marked ascites recovering from congestive heart failure. The weight decrease preceded both the venous pressure drop and the disappearance of the edema but was concordant with clearing of the ascites. The venous pressures in arms and legs approached each other as the ascites cleared (abdominal circumference).

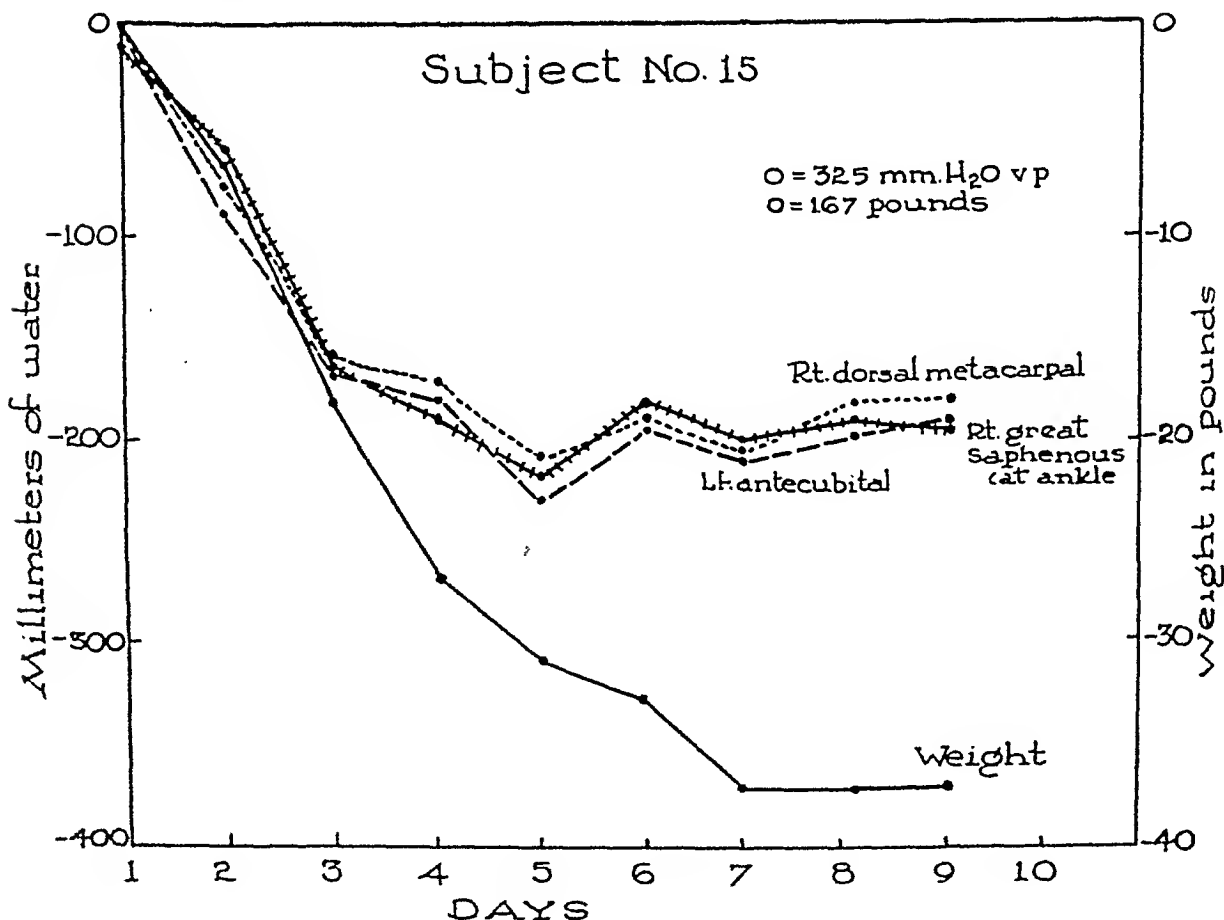


Fig. 8.—The close correlation of venous pressure in the arms and leg of a patient recovering congestive heart failure is shown; average difference, 12 mm. H₂O, with a maximum of 20.

Of the four patients showing a weight loss prior to venous pressure decrease, three had marked ascites. In these patients, initially, the pressure in the veins of the legs was higher than in the veins of the arms, but as the ascites cleared the pressures in all extremities approached each other (Fig. 7). This phenomenon has been reported.³⁸

It should be noted that in the absence of ascites simultaneous venous pressures in all extremities varied within a small range (Fig. 8). In general, the wide variation in venous pressure described for the various veins of normal persons¹⁸ was not found in diseased patients with heart disease.

SUMMARY

1. Daily determinations of weight and venous pressure were made during thirty-four significant changes in the stage of chronic congestive heart failure in twenty-three patients. This included twenty-six instances of recovery and eight of decompensation.

2. In general, the venous pressure and the weight varied concordantly. In some patients, either weight or venous pressure began changing prior to the other.

3. The findings indicate that it is not established that an elevation in either weight or venous pressure need precede the other in the development of the syndrome of chronic congestive heart failure, and that depending on the condition of the tissues, either of the two might evidence a clinically detectable rise prior to the other.

4. The behavior of the venous pressure in the patients studied confirms the value of this procedure in the diagnosis and proper clinical evaluation of congestive heart failure, especially when serial determinations are made.

5. The dependence, in part at least, of the venous pressure on the condition of the tissues is demonstrated.

CONCLUSION

In all phases of the syndrome of congestive heart failure, changes in the venous pressure and in the degree of congestion are concordant. Any initial discordance in the time relation of change in venous pressure to change in weight associated with edema can be explained by the state of those tissues affected by edema formation.

ACKNOWLEDGEMENT

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THE INFLUENCE OF SUPRADIAPHRAGMATIC SPLANCHNICECTOMY ON THE HEART IN HYPERTENSION

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SURGICAL treatment has been submitted by Peet and Isberg¹ as a measure capable of arresting and sometimes reversing, in a significant percentage of cases, the progressive deteriorating course of arterial hypertension. This opinion has been founded on the results of a long-term study of a large group of hypertensive patients treated by splanchnic resection. The operation of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic gangliectomy has been performed in more than 1,500 hypertensive patients at the University Hospital since November, 1933.

The purpose of the present study has been to obtain information concerning the cardiac aspects in arterial hypertension and how these have been influenced by surgical treatment. In order that temporary benefits from the operation be eliminated before judgment was passed, the results in only those cases operated upon five to thirteen years ago have been considered.

Studies of surgically treated hypertensive patients have suggested that the operation has influenced the destiny of the heart in hypertension. It was first recognized in 1934 that significant improvement in abnormal electrocardiograms and definite reduction in heart size occurred in some cases following splanchnicectomy. These clinical phenomena were first reported in 1939 by Braden and Kahn,² associates of Peet. In 1940, the results in 350 consecutive, surgically treated cases were evaluated by Peet, Woods, and Braden,³ and again it was pointed out that cardiac enlargement and abnormal electrocardiograms were sometimes beneficially improved after operation. Others^{4,5} have recently confirmed the effect of sympathectomy on the electrocardiogram in hypertension.

Each of the foregoing reports dealt with patients who could be followed only for a relatively short period of time. Electrocardiograms and heart size were reported as improved in cases followed only six months and longer. The present study is concerned entirely with the prolonged effects of splanchnicectomy; all patients have been followed from five to twelve years since operation.

MATERIAL

Between November, 1933, and December, 1941, 720 cases of arterial hypertension were surgically treated. The operative procedure consisted of bilateral resection of the greater, lesser, and least splanchnic nerves, and excision of the eighth, ninth, tenth, eleventh, and twelfth thoracic sympathetic ganglia. In

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the early operations, in addition to the splanchnic nerves, only the lower three dorsal ganglia were removed. The operative mortality was 3.2 per cent. During the eight years, 162 cases of malignant hypertension were operated upon, and when these are excluded, the operative mortality for the series is 1.6 per cent.

Adequate preoperative and postoperative information with respect to cardiac status has been obtained in 384 cases. Both an electrocardiogram and teleroentgenogram were procured in each of the 384 patients prior to operation; physical examinations were performed both in the departments of internal medicine and neurosurgery. Thus, a definite diagnosis concerning whether or not organic heart disease complicated the hypertension could be made in each instance. The cases of malignant hypertension, surgically treated during the same years, are not included in this study; the diagnosis of malignant hypertension was made only in those patients who showed definite papilledema of 1 diopter or more and a recent, rapidly progressive, downhill clinical course. It is felt that malignant hypertension is a distinct disease entity in itself, and a study of this disease will be reported separately.⁶

FINDINGS

Survival Rates.—Of the 384 cases of arterial hypertension in this series, 257 had definite organic heart disease prior to operation, confirmed by an abnormal electrocardiogram or teleroentgenogram showing cardiac enlargement or both. Of these patients with hypertensive heart disease, 60 per cent were alive five to twelve years postoperatively (Table I). Of the 127 hypertensive patients with normal hearts, 93 per cent were alive five to twelve years after operation. The five-to-twelve-year survival rate for the entire series of 384 is 71 per cent.

The fifty-nine persons who had sustained a cerebral accident in addition to having hypertensive heart disease prior to operation have a considerably lower survival rate than those with cardiac involvement and no cerebrovascular complication. Only 46 per cent of the former were living after five to twelve post-operative years, while 64 per cent of the latter were living.

TABLE I. SURVIVAL RATES IN THREE HUNDRED EIGHTY-FOUR CASES OF HYPERTENSION

PREOPERATIVE STATUS	CASES	DEATHS	5-TO-12 YEAR SURVIVALS
Normal heart	127	9	118 (93%)
Organic heart disease	198	71	127 (64%)
Heart disease plus cerebrovascular disease	59	32	27 (46%)
Totals	384	112	272 (71%)

The Electrocardiogram.—An electrocardiogram was considered abnormal only when one or more of the following findings was present: (1) definite left

axis deviation ($R_1 + S_3 = 25$ mm. or more); (2) inversion of T waves in Lead I, in Leads I and II, or in Leads II and III; (3) bundle branch block; and (4) evidences of previous myocardial infarction.

An abnormal electrocardiogram was considered "significantly improved" five years and more after operation only when: (1) inverted T waves returned to an upright configuration with an amplitude of 1 mm. or more, or (2) 30° change of electrical axis toward normal occurred with reduction of 8 mm. or more in the value of $R_1 + S_3$. An electrocardiogram with both abnormal T waves and left axis deviation was considered "improved" when either one of these criteria was fulfilled.

A postoperative electrocardiogram was considered to be "worse" when any one of the following appeared: (1) 1 mm. or more depression of a previously upright or flat T wave in Lead I or II; (2) a 30° change of electrical axis toward abnormal, with increase of 8 mm. or more in the value of $R_1 + S_3$; (3) evidences of myocardial infarction; and (4) bundle branch block.

Two hundred nineteen patients had abnormal preoperative electrocardiograms; 60 per cent of these persons were still living five to twelve years post-operatively. Of the 165 hypertensive patients with normal electrocardiograms, 85.5 per cent were alive five years and more after operation.

Table II enumerates the incidence of the various electrocardiographic abnormalities in this series, the subsequent deaths with each abnormality, and the electrocardiographic status of the living patients five years and more after operation. It is seen that patients with inverted T waves in both Leads I and II have the highest death rate; but when these patients survive five years and more their tracings are likely to be "significantly improved."

One hundred eighty-four living patients had recent electrocardiograms taken, five to twelve years after operation (Table III). Of the eighty-three who had abnormal tracings prior to operation, 41 per cent now show "significant improvement," 55.4 per cent show no change, and 3.6 per cent have progressed to worse changes. All patients who had sustained a coronary occlusion or were ever given digitalis were automatically excluded from the "significantly improved" classification.

Of the 101 patients whose electrocardiograms were normal preoperatively, 94 per cent have maintained an unchanged, normal tracing during the long post-operative period; in 6 per cent the tracing have become abnormal. Six series of electrocardiograms are shown in Figs. 1, 2, 3, 4, 5, and 6. All were abnormal before operation and improved notably after operation.

There is a definite correlation between postoperative improvement in the electrocardiogram and postoperative reduction in blood pressure. Of the thirty-four patients who had an abnormal preoperative electrocardiogram and who have maintained a "significantly improved" tracing for five years and more after operation, six have maintained normal blood pressure levels (140/90 or less),

and twenty-six have maintained a significant reduction of 15 mm. or more diastolic pressure during the postoperative period. Only two patients with improved electrocardiograms showed no improvement in diastolic pressure (Table IV).

TABLE II. THE ELECTROCARDIOGRAM IN THREE HUNDRED EIGHTY-FOUR HYPERTENSIVE PATIENTS

[PREOPERATIVE STATUS	CASES	DEATHS	PATIENTS ALIVE FIVE TO TWELVE YEARS POSTOPERATIVELY				
			CASES LIVING	SIGNIFICANT IMPROVEMENT IN ECG	NO SIGNIFICANT CHANGE	WORSE	NO FOLLOW-UP ECG
Normal ECG	165	24	141	—	95	6	40
Abnormal ECG	219	88	131	34	46	3	48
Inverted T ₁	18	6	12	4	3	0	5
Inverted T ₁ and T ₂	54	27	27	13	4	0	10
Inverted T ₂ and T ₃	14	3	11	2	3	1	5
Definite L.A.D.	42	10	32	2	18	2	10
Both inverted T waves and definite L.A.D.	75	37	38	13	9	0	16
Bundle branch block	5	2	3	0	3	0	0
Evidences of previous myocardial infarction	11	3	8	0	6	0	2

TABLE III. THE INFLUENCE OF SURGICAL TREATMENT ON THE ELECTROCARDIOGRAMS OF ONE HUNDRED EIGHTY-FOUR PATIENTS FIVE TO TWELVE YEARS AFTER OPERATION

PREOPERATIVE STATUS	CASES	POSTOPERATIVE STATUS		
		SIGNIFICANTLY IMPROVED	NO SIGNIFICANT CHANGE	WORSE
Normal ECG	101	—	95 (94%)	6 (6%)
Abnormal ECG	83	34 (41%)	46 (55.4%)	3 (3.6%)

None of the electrocardiographic abnormalities which occurred in this series can be considered a contraindication to surgical treatment. The death rate in the presence of any one of the abnormalities is not so great as to render

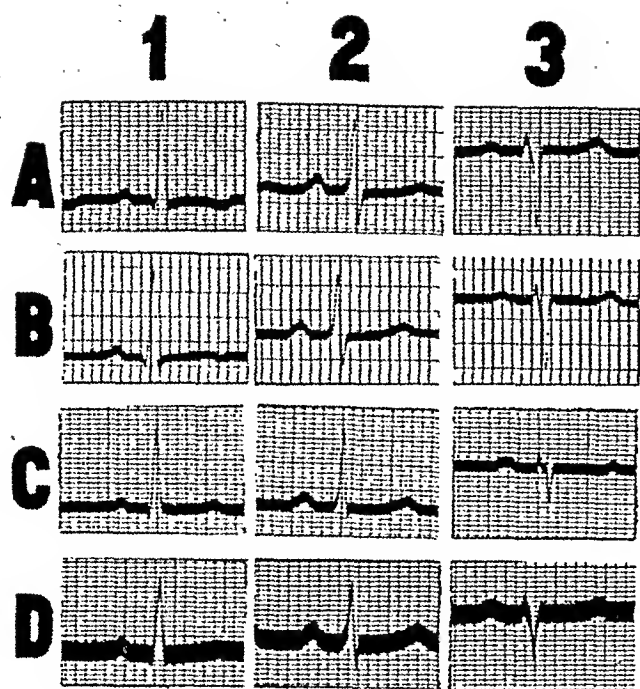


Fig. 1.—Case 1. A, (April 11, 1939) preoperative ECG; left axis deviation and inverted T waves in Lead I. Splanchnicectomy was performed on April 15, 1939. B, (Oct. 18, 1939) six months postoperative; T waves in Lead I are now upright. C, May 9, 1940. D, (April 13, 1944) five years postoperative; upright T waves maintained in Lead I, and left axis deviation is less marked than in preoperative tracing.

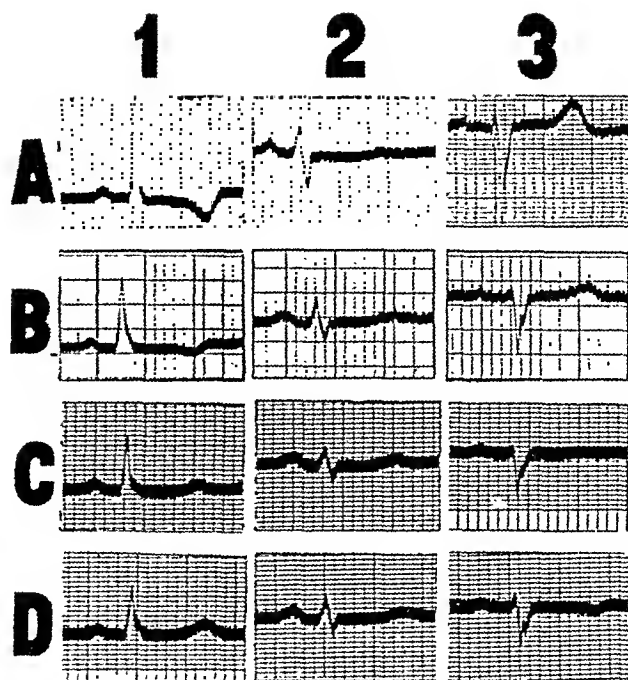


Fig. 2.—Case 2. A, (Oct. 18, 1940) preoperative ECG; definite left axis deviation, inverted T waves in Lead I, and flat T waves in Lead II. Splanchnicectomy was performed on Oct. 24, 1940. B, (April 3, 1941) six months postoperative; T waves in Lead I are less deeply inverted than previously. C, (Sept. 1, 1944) four years postoperative; shows almost complete retrogression of the 1940 ECG changes; T waves are now normal and the slight axis deviation is within normal limits. D, (Sept. 27, 1945) five years postoperative; ECG remains within normal limits.

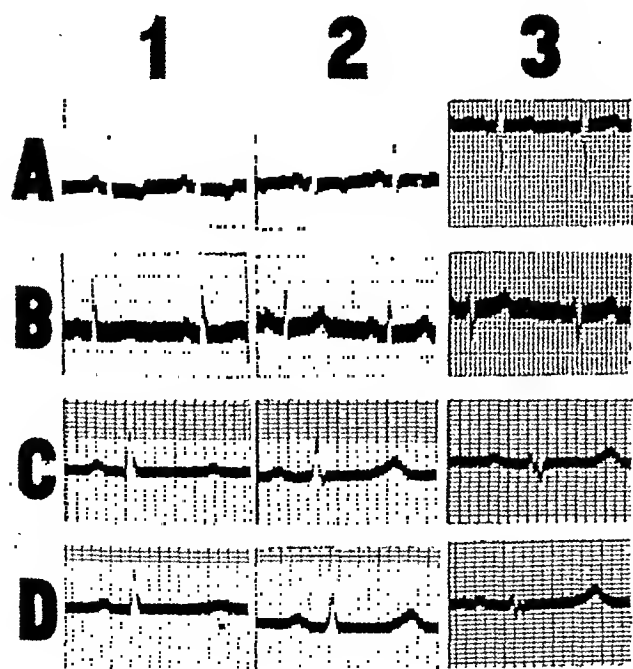


Fig. 3.—Case 3. A, (Nov. 22, 1934) preoperative ECG; definite left axis deviation and inverted T waves in Lead I. Splanchnicectomy was performed on Dec. 3, 1934. B, (Sept. 28, 1937) three years postoperative; slight left axis deviation and upright T waves in Lead I. C, Aug. 25, 1938. D, (Aug. 27, 1940) six years postoperative; normal ECG. The Q-T interval of the last two tracings is not abnormally long when compared to the heart rate which was 58 per minute.

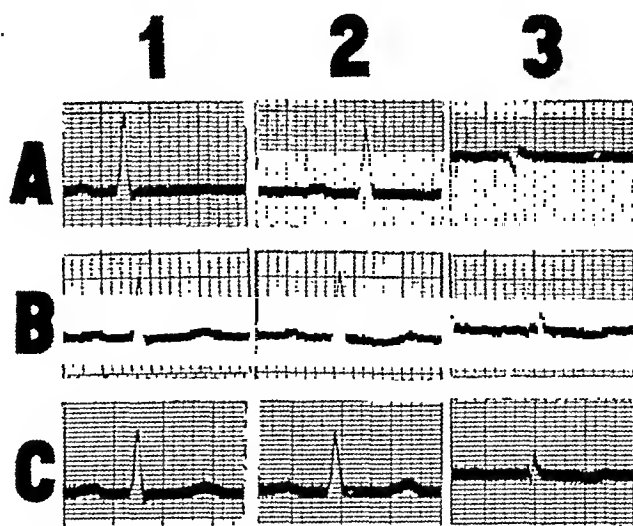


Fig. 4.—Case 4. A, (April 2, 1940) preoperative ECG; flat T waves in Lead I and slight inversion of T waves in Leads II and III. Splanchnicectomy was performed on April 11, 1940. B, (Nov. 6, 1940) six months postoperative; slight inversion of T waves in Leads II and III. C, (July 26, 1945) five years postoperative; normal ECG.

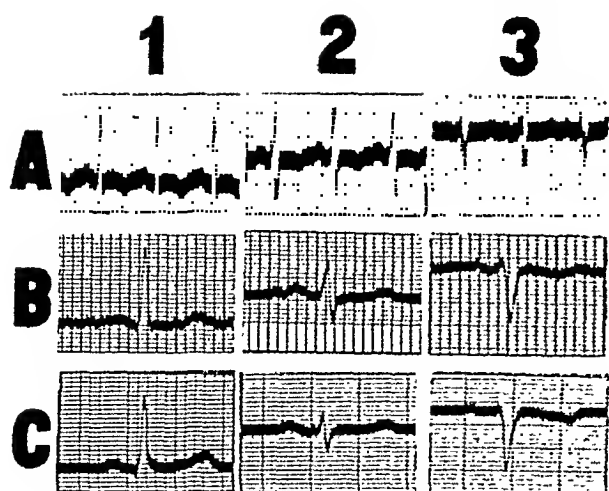


Fig. 5.—Case 5. A, (March 1, 1937) preoperative ECG; left axis deviation and inverted T waves in Leads I and II. Splachnicectomy was performed on March 6, 1937. B, (Sept. 8, 1938) eighteen months postoperative; T waves are now normal. C, (Aug. 7, 1946) normal T waves have been maintained for nine years since operation.

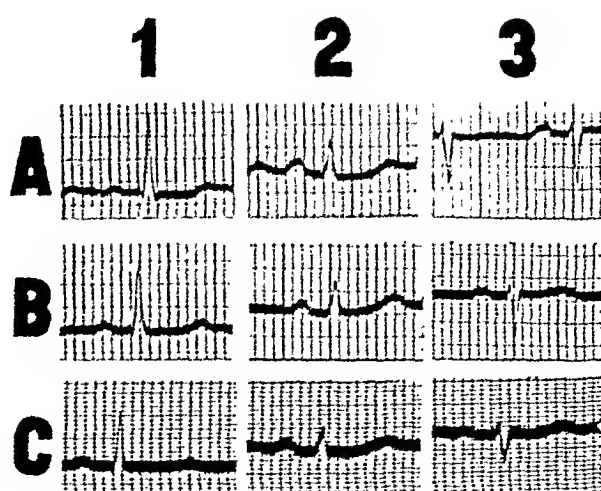


Fig. 6.—Case 6. A, (Aug. 4, 1938) preoperative ECG; definite left axis deviation with depressed RS-T segments and inverted T waves in Leads I and II. Splachnicectomy was performed on Aug. 18, 1938. B, (April 11, 1939) eight months postoperative; T waves are now upright in Leads I and II. C, (Aug. 9, 1946) eight years postoperative; ECG is within normal limits; T waves are upright and axis deviation is no longer outside normal limits.

splanchnic resection futile, and each of the abnormalities, except bundle branch block and previous myocardial infarction, potentially may be significantly improved following operation.

Heart Size.—Heart size in this series has been followed by serial teleroentgenograms taken before and after splanchnic resection. The prediction tables of Hodges, P. C., and Eyster⁷ for frontal area, and the prediction tables of Hodges, F. J., and Eyster⁸ for transverse diameter have been used. Table V lists the criteria for determining relative extent of cardiac enlargement on the basis of the per cent variation from predicted normal.

TABLE IV. CORRELATION OF POSTOPERATIVE ECG CHANGE WITH POSTOPERATIVE BLOOD PRESSURE CHANGE IN EIGHTY-THREE PATIENTS WHO HAD ABNORMAL ECG PREOPERATIVELY

POSTOPERATIVE ECG	CASES	POSTOPERATIVE BLOOD PRESSURE		
		REDUCED TO NORMAL	15 MM. OR MORE REDUCTION IN DIASTOLIC PRESSURE	NO CHANGE OR WORSE
Significant improve- ment	34	6	26	2
No significant change	46	2	28	16
Worse	3	0	0	3

In order for a postoperative teleroentgenogram to be considered as demonstrating "significant decrease" in heart size from the preoperative state, there must have occurred a 10 per cent or more decrease in frontal area or transverse diameter variation and change to the next category toward normal, according to Table V. The criterion for "significant increase" is that a 10 per cent or more increase in frontal area or transverse diameter variation has occurred.

TABLE V. CRITERIA FOR DETERMINING EXTENT OF CARDIAC ENLARGEMENT

HEART SIZE	VARIATION FROM PREDICTED NORMAL	
	CARDIAC AREA	TRANSVERSE DIAMETER
Upper limit of normal	+ 10%	+ 10%
Slight cardiac enlargement	11% to 20%	11% to 20%
Moderate cardiac enlargement	21% to 50%	21% to 50%
Marked cardiac enlargement	Greater than 50%	Greater than 50%

Cardiac enlargement was present in 177 cases, or 43 per cent of the series. Of the hypertensive subjects in whom an enlarged heart was demonstrated, 50 per cent did not survive five to twelve years after the operation. It is seen that in hypertensive heart disease, patients with cardiac enlargement have a somewhat poorer prognosis than those with an abnormal electrocardiogram. Of those with normal sized hearts, 88.4 per cent were living (Table VI).

TABLE VI. HEART SIZE IN THREE HUNDRED EIGHTY-FOUR HYPERTENSIVE PATIENTS

PREOPERATIVE STATUS	CASES	DEATHS	PATIENTS ALIVE 5 TO 12 YEARS POSTOPERATIVELY				
			CASES LIVING	SIGNIFICANT DECREASE IN HEART SIZE	NO CHANGE	INCREASE IN HEART SIZE	NO FOLLOW-UP TELEROENTGENOGRAM
Normal heart size	207	24	183	—	123	10	50
Cardiac enlargement	177	88	89	25	26	6	32
Slight cardiac enlargement	83	33	50	11	16	5	18
Moderate cardiac enlargement	76	38	38	14	10	1	13
Marked cardiac enlargement	18	17	1	—	—	—	1

Teleroentgenograms were recently obtained in 190 living patients five to twelve years after operation. Of the fifty-seven patients with preoperative cardiac enlargement, significant decrease in heart size was demonstrated in 44 per cent, 45.6 per cent showed no change, and in 10.4 per cent, further increase in size had occurred (Table VII). Serial teleroentgenograms of four patients whose heart size decreased significantly after operation are shown in Figs. 7, 8, 9, and 10.

TABLE VII. THE INFLUENCE OF SURGICAL TREATMENT ON HEART SIZE, MEASURED ON TELEROENTGENOGRAMS OF ONE HUNDRED NINETY PATIENTS FIVE TO TWELVE YEARS AFTER OPERATION

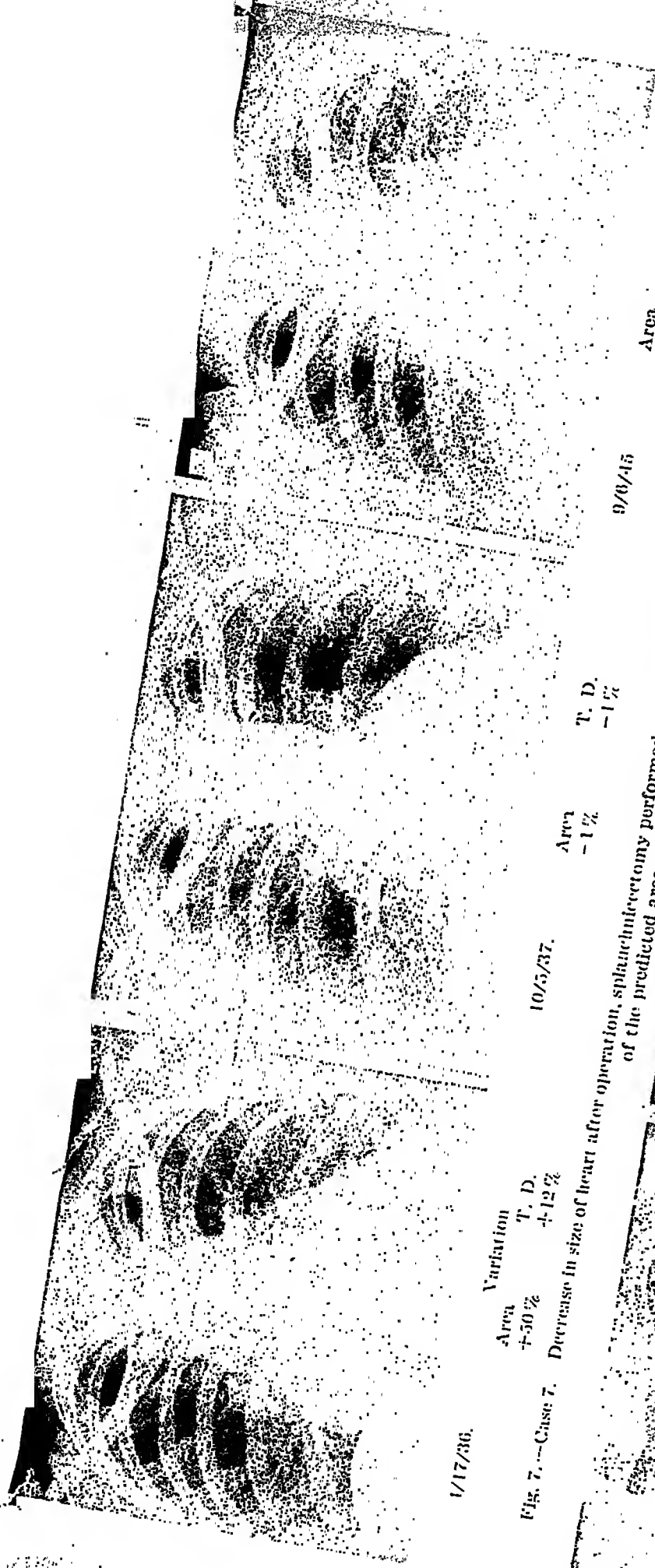
PREOPERATIVE STATUS	CASES	POSTOPERATIVE STATUS		
		SIGNIFICANT DECREASE IN HEART SIZE	NO CHANGE	SIGNIFICANT INCREASE IN HEART SIZE
Normal heart size	133	—	123 (92.5%)	10 (7.5%)
Cardiac enlargement	57	25 (44%)	26 (45.6%)	6 (10.4%)

Of the 133 patients with normal heart size prior to operation, 92.5 per cent maintained an unchanged normal status for five years and more. Cardiac enlargement occurred during the long postoperative period in 7.5 per cent of those who had hearts of normal size before splanchnic resection.

It appears that reduction in blood pressure is necessary in order for a significant decrease in heart size to occur. In all twenty-six persons in whom definite decrease in heart size was demonstrated, blood pressure levels have either been reduced to within normal range, or a significant reduction of 15 mm. or more in diastolic pressure has been maintained (Table VIII).

TABLE VIII. CORRELATION OF POSTOPERATIVE HEART SIZE CHANGE WITH POSTOPERATIVE BLOOD PRESSURE CHANGE IN FIFTY-SEVEN PATIENTS WHO HAD PREOPERATIVE CARDIAC ENLARGEMENT

POSTOPERATIVE HEART SIZE	CASES	POSTOPERATIVE BLOOD PRESSURE		
		REDUCED TO NORMAL	15 MM. OR MORE REDUCTION IN DIASTOLIC PRESSURE	NO CHANGE OR WORSE
Significant decrease in size	25	5	20	0
No change	26	1	15	10
Increase in heart size	6	0	1	5



1/17/36.

Variation
Area +50 %
T. D. +12 %

10/5/37.

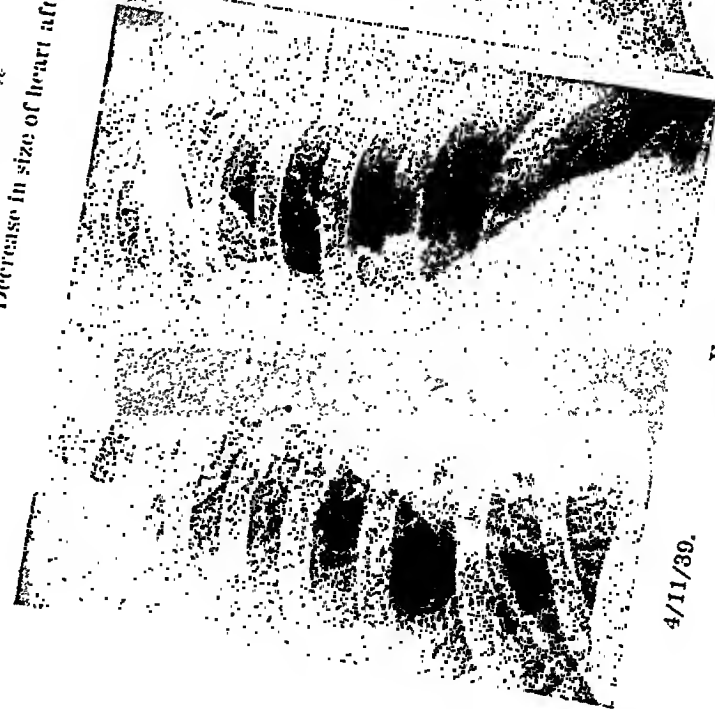
Area -1 %
T. D. -1 %

9/6/45

Area +4 %
T. D. +2 %

of the predicted area as transverse diameter.

The heart size is expressed in percentage



4/11/39.

Variation
Area +13 %
T. D. +8 %

10/18/39.

Area -6 %
T. D. -5 %

1/13/44.

Area -8 %
T. D. -7 %

Fig. 8.—Case 8. Splanchnicectomy performed on April 15, 1939.



1/17/38.
Area
+16%
Variation
T. D.
+11%

9/23/38.

Area
-3%

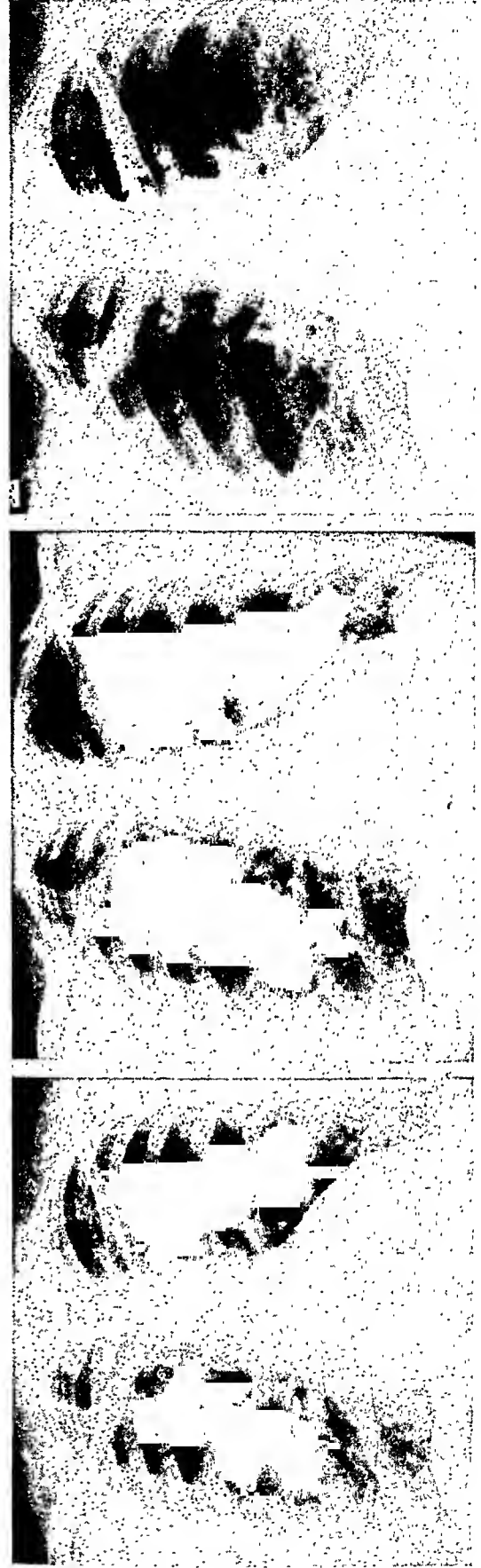
T. D.
-6%

5/28/45.

Area
+6%

T. D.
-19%

Fig. 9.—Case 9. Splanchnicectomy performed on Feb. 4, 1938.



3/17/38.
Area
+23%
Variation
T. D.
+20%

4/12/39.

Area
+4%

T. D.
+6%

8/23/45.

Area
-2%

T. D.
+8%

Fig. 10.—Case 10. Splanchnicectomy performed on March 28, 1938.

Splanchnic resection has nothing to offer the hypertensive patient with *marked* cardiac enlargement. When the variation above the predicted normal is greater than 50 per cent for area or transverse diameter, the outlook is grave, and it cannot be influenced by splanchnicectomy. Of the eighteen patients who had marked cardiac enlargement, only one has survived five years.

Cardiac Symptoms.—One or more of the cardiac symptoms of exertional dyspnea, paroxysmal nocturnal dyspnea, palpitation, swollen ankles, and anginal seizures were present in 54 per cent of the series. Eighty-five per cent of the patients complaining of cardiac symptoms had definite organic heart disease, confirmed by an abnormal electrocardiogram, by a teleroentgenogram showing cardiac enlargement, or by both.

Of 162 patients who complained of exertional dyspnea, 100 had definitely enlarged hearts. Of the patients with exertional dyspnea, 38.3 per cent did not have cardiac enlargement (Table IX).

Fifty-nine per cent of the patients with cardiac complaints have survived five to twelve postoperative years. Of the 124 persons who had preoperative symptoms and who were still living, 60 per cent were improved, 37 per cent have obtained no relief, and 3 per cent were worse.

The patient with paroxysmal nocturnal dyspnea has very little to gain from surgical treatment of his hypertension. There were twenty-four cases with this complaint, and only three survived five years or more. Each of the twenty-four cases had an abnormal electrocardiogram and all but one also had cardiac enlargement.

Sixty-eight patients complained of characteristic anginal seizures, and 84 per cent of these had organic heart disease, confirmed by abnormal electrocardiogram or cardiac enlargement by teleroentgenogram or both. Sixty-two per cent of the patients with angina survived five to twelve years, and more than one-half of those still living have obtained definite relief from the seizures. Fourteen patients have been completely relieved of angina for five years or more since splanchnic resection.

Of the 174 hypertensives who had no cardiac complaints, 85 per cent are still living. Ninety-three per cent still have no cardiac symptoms, while 7 per cent have developed symptoms during the long postoperative period.

Physical Signs.—Abnormal cardiac physical signs were present in 160 patients, or 24 per cent of the series, and 84 per cent of these had confirmed organic heart disease (Table X).

Fifty-eight per cent of patients with a systolic murmur and 60.6 per cent of patients with an accentuated aortic second sound were living five to twelve years after operation. This approximates the overall 60 per cent survival rate of the group with hypertensive heart disease.

Only 23.3 per cent of the patients with gallop rhythm and 33.2 per cent of those with an accentuated pulmonic second sound have lived five to twelve years

TABLE IX. CARDIAC SYMPTOMS

PREOPERATIVE STATUS	CASES	CONFIRMED HEART DISEASE				DEATHS	PATIENTS ALIVE 5 TO 12 YEARS POSTOPERATIVELY			
		CASES	BOTH ABNORMAL ECG AND CARDIAC ENLARGEMENT	ABNORMAL ECG ONLY	CARDIAC ENLARGEMENT ONLY		CASES	IMPROVED	SAME	WORSE
No cardiac symptoms	174	78	30	32	16	26	148	—	138	10
Symptoms present	210	179	109	48	22	86	124	74	46	4
Exertional dyspnea	162	137	85	37	15	74	88	48	37	3
Paroxysmal nocturnal dyspnea	24	24	23	1	0	21	3	2	1	0
Palpitation	50	39	22	13	4	18	32	21	11	0
Swollen ankles	30	27	21	5	1	16	14	8	6	0
Angina	68	57	37	16	4	26	42	23	18	1

TABLE X. PHYSICAL SIGNS

PREOPERATIVE STATUS	CASES	CONFIRMED HEART DISEASE				DEATHS	PATIENTS ALIVE 5 TO 12 YEARS POSTOPERATIVELY			
		CASES	BOTH ABNORMAL ECG AND CARDIAC ENLARGEMENT	ABNORMAL ECG ONLY	CARDIAC ENLARGEMENT ONLY		CASES	IMPROVED	SAME	WORSE
No physical signs	224	123	50	49	24	45	179	—	170	9
Physical signs present	160	134	89	31	14	67	93	13	78	2
Systolic murmur	86	70	45	15	10	36	50	6	44	
Accentuated A ₂	61	50	33	8	9	24	37	5	32	
Accentuated P ₂	6	6	3	1	2	4	2	0	2	
Gallop	30	30	25	5	0	23	7	5	2	

following operation. Although splanchnic resection offers only a slim chance for prolonged survival to these patients, the presence of either one of these two signs does not contraindicate operation.

Congestive Heart Failure.—Sixteen patients in congestive heart failure were digitalized prior to splanchnicectomy. Only five of these patients were living after five years or more. One patient died on the day following operation.

The hypertensive cardiac patient who requires digitalization has a grave outlook. But since such a patient stands one chance in three for prolonged survival following splanchnic resection, he should not be denied the operation once he is properly digitalized.

Coronary Occlusion.—Eleven patients who had had a coronary occlusion with myocardial infarction were subsequently treated by splanchnicectomy for their hypertensive disease. Eight of these persons were still living five to nine years after operation. The three deaths each resulted from a subsequent coronary occlusion, one to four years after operation.

This prolonged survival of 72.7 per cent of the hypertensive patients who had also had a coronary occlusion should lead one to consider seriously splanchnicectomy in hypertensive patients six to twelve months following a coronary occlusion.

Coronary occlusion has occurred in twenty-four patients out of the entire series from three months to eleven months after operation. Six have survived myocardial infarction, and were still living five to ten years after splanchnic resection. It has been the cause of death in eighteen cases; 17 per cent of the 112 deaths in this series have resulted from coronary occlusion. Goldring and Chasis⁹ have compiled the causes of death in patients with hypertensive disease as reported by various authors, and coronary thrombosis accounted for 13.6 per cent of the total deaths in six different series.

Of the twenty-four cases who sustained a coronary occlusion subsequent to splanchnicectomy, twenty had both an abnormal electrocardiogram and cardiac enlargement before operation. Five had anginal seizures preoperatively, and in four patients gallop rhythm was present prior to splanchnic resection.

DISCUSSION

The study of cardiac aspects in 384 cases of arterial hypertension treated by splanchnic resection five to thirteen years ago have revealed the following:

1. Sixty per cent of patients with hypertensive heart disease were still living five to twelve years after splanchnicectomy.
2. Ninety-three per cent of hypertensive patients with normal hearts were still living five to twelve years after operation.
3. Patients whose electrocardiograms show inverted T waves in both Leads I and II, or both definite left axis deviation and abnormal T waves, have a 50 per cent chance for prolonged survival following splanchnicectomy.

4. Of the patients still alive, 41 per cent of those with abnormal preoperative electrocardiograms recently showed significant improvement in their tracings five years or more after operation, and 44 per cent of those with preoperative cardiac enlargement recently showed significant decrease in heart size.

5. Practically all patients who have shown improvement in electrocardiogram or decrease in heart size have maintained a significant reduction in blood pressure.

6. Fifty per cent of hypertensive patients in whom an enlarged heart was demonstrated have not survived five to twelve years.

7. Splanchnic resection is of no avail in cases of marked cardiac enlargement with a variation greater than 50 per cent of predicted normal for frontal area or transverse diameter.

8. The patient with paroxysmal nocturnal dyspnea has little chance for benefit from splanchnic resection; only 12.5 per cent survived five years or more.

9. Anginal seizures were frequently relieved following splanchnicectomy.

10. Of patients with gallop rhythm prior to operation, 23.3 per cent have survived five years or more.

11. The hypertensive patient in congestive heart failure which requires digitalization preparatory to splanchnicectomy stands one chance in three for prolonged survival following operation.

12. Eight out of eleven hypertensive patients who had had a coronary occlusion and were subsequently treated with splanchnic resection were still living five to nine years after operation.

Canabal and associates¹⁰ have recently supplied valuable information concerning the spontaneous evolution of the electrocardiogram in hypertension. They reported on a control series of fifty cases of hypertension with electrocardiograms taken over a period of five years or more. They found that in 10 per cent of the cases there was questionable-to-slight improvement of the electrocardiogram; that in 40 per cent, the tracings remained unchanged; and that in 50 per cent, they became worse. The spontaneous trend of the electrocardiogram in hypertension is to become worse as time goes on.

When one compares this control group with the eighty-three hypertensive patients who had abnormal electrocardiograms prior to splanchnic resection, and of whom 41 per cent showed significant improvement in their tracings five to twelve years later, and of whom only 3.6 per cent developed more serious electrocardiographic changes, then one may justifiably state that splanchnicectomy has beneficially influenced the destiny of the hypertensive patients with abnormal electrocardiograms who have been fortunate enough to have lived five years and longer after operation.

There were 127 hypertensive patients who showed no evidences of cardiac disease at the time of operation. Nine subsequently died, and eight, who were still living, have developed heart disease, confirmed by an abnormal electrocardiogram or cardiac enlargement by teleroentgenogram or by both. Of the

hypertensive patients with normal hearts prior to operation, 86.6 per cent were living and had maintained a normal cardiac status for five to twelve years; 6.4 per cent were still living but had progressed to heart disease; and 7 per cent were dead. Has splanchnic resection significantly arrested progression to heart disease in hypertensive patients with normal hearts? Although the preceding figures appear appealingly good, no definite statement can as yet be made, for no appropriate control group is available for comparison.

Has splanchnic resection prolonged the lives of patients with hypertensive heart disease? Again no definite statement can be made even though the statistics of this series evoke a sympathetic response. The literature is inadequate concerning the life history of hypertensive patients with organic heart disease, and no fair comparisons can be made.

There are several reports in the literature on survival in hypertension, but in none are the hypertensive patients with heart disease separated from those with normal hearts. In Janeway's¹¹ series of 458 hypertensive patients, one-half of the men died within four years and one-half of the women within five years; by the tenth year, one-half of the remainder had died. Hamman¹² had a 78 per cent mortality at the end of ten years. King and associates¹³ followed 481 patients for ten to sixteen years, and the mortality was 73 per cent. In one-half of their cases, the discovery of hypertension was purely an incidental finding.

Wagener and Keith¹⁴ have presented a five-to-nine-year follow-up study of 219 cases of arterial hypertension, and they have offered the series as a control for any specific form of therapy. Their cases are classified according to retinal changes; the incidence of heart disease in this series is not known. One hundred forty-six of their patients had malignant hypertension. The remaining seventy-three patients form a series comparable to the 384 patients presented in this paper. Of their hypertensive patients without papilledema, 24.6 per cent have survived five to nine years since the initial examination. Of the 384 hypertensives without papilledema in our series, 71 per cent have survived five to twelve years since operation. It appears that splanchnic resection may have beneficially influenced survival in hypertensive patients.

SUMMARY

This is a study of the cardiac aspects in 384 patients with arterial hypertension, treated surgically by the operation of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. The findings suggest that this surgical treatment may have beneficially influenced the destiny of a significant percentage of hypertensive patients.

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THE ELECTROCARDIOGRAM OF MAN IN SEMISTARVATION AND SUBSEQUENT REHABILITATION

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FROM the current textbooks and monographs on cardiology it seems to be believed that inanition has no significant effects on the heart and its function. Elsewhere, however, we have shown that there are, in fact, profound changes in the size and function of the heart in semistarvation and subsequent rehabilitation.¹ The present paper is an analysis of the associated electrocardiographic findings. While this material has primary reference to famine conditions, it should be noted that similar physiologic states occur in all wasting diseases; indeed, the majority of chronic illnesses tend to produce changes in this direction.

The literature on electrocardiographic changes in chronic semistarvation and prolonged undernutrition is very small. Benedict and co-workers² reported that the electrocardiograms in their experiments on undernutrition were within "normal" limits, but no quantitative analysis was made. The degree of semistarvation attained in Benedict's series was mild compared to that in the series to be reported here and to the conditions in famine areas. The remaining scanty data in the literature were obtained from the uncontrolled conditions of war and associated famine; electrocardiograms from the prestarvation state were not available.

Electrocardiographic material was obtained by Tur³ during the siege of Leningrad in 1941 and 1942. In forty severely undernourished patients, the majority showed sinus bradycardia, right axis shift, and low QRS voltage. In deteriorating patients, there was a progressive tendency to lower T-wave amplitude in the standard leads. In a later group of twenty-four patients, who had presumably suffered more prolonged but less acute inanition, the majority showed subnormal T-wave amplitudes and these were thought to have prognostic significance.

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Cardozo and Eggink⁴ found low voltage and sinus bradycardia in twenty-nine cases of severe undernutrition. In addition, the Q-T interval was prolonged, both absolutely and in relation to the cycle rate.

Ellis⁵ made electrocardiographic studies on four repatriated prisoners of war, immediately after liberation and during three weeks of rehabilitation; these men were in an advanced state of semistarvation. The most prominent feature was a tremendous prolongation of the Q-T interval. In three cases, the P wave was superimposed on the descending limb of a rounded T wave, and in two cases the S-T segment was depressed. Several other features are discernible in the electrocardiograms reproduced by Ellis. All four patients had a right axis shift and the T waves were small or became small during refeeding. The QRS amplitude decreased during treatment in three patients and was rather low at all times in the fourth patient. In the most cachectic patient a pulsus trigeminus, due to premature ventricular beats, disappeared with refeeding.

The material presented here was obtained from thirty-two young men, previously normal, who underwent twenty-four weeks of semistarvation (after a control period of twelve weeks), and during thirty-two subsequent weeks of rehabilitation. During the semistarvation period, the men lost from 27 to 65 pounds, representing an average of 24 per cent of their original weight. Further details are given elsewhere.^{1,6-8} The clinical picture closely simulated that seen in many liberated areas in Europe in the spring of 1945.

METHOD

General Procedure and Experimental Arrangement.—Thirty-two normal young men (age range from 20 to 33 years) resided in the laboratory on a controlled regimen of diet and activity. During a control period (C)* of three months, they were kept at a maintenance diet averaging 3,490 calories. For 167 subsequent days they subsisted on a European type of famine diet, averaging daily 1,660 calories, including 30 Gm. of fat, 54 Gm. of protein, 1.29 mg. of thiamine, 0.71 mg. of riboflavin, and 20.7 mg. of niacin.

At the end of the semistarvation period, the thirty-two subjects were subdivided into four groups for the first twelve weeks (to R12) of rehabilitation (Groups Z, L, G, and T), who received diets differing in steps of 400 calories daily; Group Z averaged 2,500 calories daily in this period. After R12, there were no diet restrictions.

Although electrocardiograms were taken more frequently, we have restricted the detailed analysis to the following periods, which characterize the general trend of the changes during semistarvation: control (C), twelfth and twenty-fourth weeks of semistarvation (S12 and S24), and the twelfth week of rehabilita-

*Throughout the paper, the following legend will be used:

C = control period.

S12 = twelfth week of starvation.

R12 = twelfth week of rehabilitation.

tion (R12). The average body weights of the thirty-two men were 70.0, 56.9, 53.2, and 59.4 kg. at these several times, respectively. Twenty of these men were re-examined after thirty-two weeks of rehabilitation (R32); at that time their body weights, in most cases, exceeded their original control weights.

Electrocardiographic Procedure.—The three standard leads were taken, together with heart sound records, during arrested respiration. An external voltage calibration was used before and after each series, in addition to that incorporated in the instrument (Sanborn). The speed was similarly checked independently. The duration of mechanical systole was calculated as the interval between the start of the major oscillations of the first heart sound and the beginning of the second heart sound. Both Q-T interval and mechanical systole were averaged from five beats, usually in Lead II. The constant K was calculated both for Q-T (K_{Q-T}) and mechanical systole duration (K_{SYST}), using the formula $K = \frac{Q-T \text{ (or systole)}}{\sqrt{R-R}}$. The average heart rate was calculated from ten

beats; in addition, the shortest and longest R-R intervals of the whole record were measured. Their difference, absolute and in percentage of the average heart rate, was used as a criterion of arrhythmia. The amplitudes of the P wave, the QRS complex, and the T wave were measured in all leads. The QRS axis and the T axis were calculated, using Dieuaide's procedure. For estimation of the overall magnitude of the QRS complex and the T wave, the sum of the amplitudes in Leads I, II, and III was calculated. The symbols Σ_{QRS} and Σ_T are used to express these values.

After Lead II was taken with arrested respiration, the effect of maximum inspiration was recorded in the same lead. Early and late effects, especially on intervals, were analysed. The statistical significance of the changes in semi-starvation and rehabilitation was calculated by means of the T-test.^{9,10}

RESULTS

Interval Changes.—Tables I and II show the average interval changes (heart rate, Q-T interval, systole duration, K_{Q-T} and K_{SYST}) during starvation and thirty-two weeks of rehabilitation. The P-R interval, QRS interval, and duration of the P wave did not change significantly during starvation and rehabilitation and are, therefore, not included in the tables.

Table I shows the absolute values and standard deviations for the total group of thirty-two subjects for the periods C, S12, S24, and R12 and for twenty subjects for the periods C, S24, R12, and R32. Table II shows the differences between the various periods, calculated from Table I. The values of both groups coincide very closely for the periods C, S24, and R12, so that probably the changes at R32 of the group of twenty subjects are representative for the total group of thirty-two subjects.

The slow average heart rate (55.2 beats per minute) during the control period agrees well with many observations on healthy young men made in this

TABLE I. HEART RATE, Q-T INTERVAL, AND SYSTOLE DURATION IN SEMISTARVATION AND REHABILITATION. MEAN VALUES AND STANDARD DEVIATIONS OF THIRTY-TWO AND TWENTY SUBJECTS

FUNCTION	NO. OF SUB- JECTS	CONTROL		S12		S24		R12		R32	
		M	$\pm \sigma$	M	$\pm \sigma$	M	$\pm \sigma$	M	$\pm \sigma$	M	$\pm \sigma$
Heart rate (beats/min.)	32 20	55.20 54.9	6.49 —	35.3 —	4.96 —	37.3 37.5	5.15 —	49.2 50.0	6.56 —	— 58.7	— 5.03
Range of heart rate absolute	32 20	9.50 9.8	4.16 —	3.1 —	1.16 —	3.4 3.3	1.27 —	7.6 7.2	4.50 —	— 10.4	— 2.66
Range in per cent of aver- age heart rate	32 20	14.7 15.3	— —	8.1 —	— —	8.8 8.8	— —	14.1 13.8	— —	— 17.8	— 4.07
Absolute Q-T (sec. x 100)	32 20	35.8 36.1	2.69 —	46.1 —	8.63 —	45.1 45.8	2.55 —	41.3 41.4	2.27 —	— 39.8	— 2.71
Absol. mechan. systole dura- tion (sec. x 100)	32 20	32.5 —	2.46 —	39.3 —	2.39 —	39.3 —	2.41 —	37.2 —	2.02 —	— —	— —
K_{Q-T} (x 100) (Q-T/R-R ²)	32 20	37.01 37.03	1.8 —	36.54 —	1.6 —	36.34 36.43	2.4 —	38.18 37.94	1.7 —	— 38.69	— 2.2
K_{SYST} (x 100)	32	33.55	1.6	31.09	1.3	31.55	1.6	34.35	1.5	—	—

laboratory during recent years. The heart rate slowed to 37.3 beats at the end of the semistarvation; it increased again during rehabilitation, but was still below the control value at the twelfth week of rehabilitation. However, a further increase occurred from R12 to R32, and this change was statistically highly significant. The pulse rate at R32 even exceeded the initial rate (C), and this difference was statistically highly significant.

The decrease of the heart rate was associated with a narrowing of the range of the heart rate (variability within the electrocardiogram). This is true for the absolute range as well as for the variability in percentage of the average heart rate. The heart beat is more regular in the starved subject than it is in a normal subject. A pronounced sinus arrhythmia which was present in a few subjects in the control period disappeared completely during semistarvation. In the rehabilitation period the range increased with the heart rate again and sinus arrhythmia returned in those subjects who had sinus arrhythmia before starvation. Expressed as percentage (Table II), the decrease of the range (variability) of the heart rate in starvation (and the increase in rehabilitation) exceeded the decrease of the heart rate.

The absolute Q-T interval and mechanical systole duration increased during semistarvation, as should be expected from the lengthening of the cycle. As shown by the changes of K_{Q-T} and K_{SYST} during starvation and rehabilitation, the changes in the Q-T interval and in the mechanical systole duration lagged

TABLE II. DIFFERENCES OF INTERVALS, ABSOLUTE AND IN PERCENTAGE OF THE PRECEDING REFERENCE PERIOD
(THE VALUES CORRESPOND TO THOSE OF TABLE I)

FUNCTION	NO. OF SUB- JECTS	$\Delta C-S12$		$\Delta C-S24$		$\Delta R12-S24$		$\Delta R32-S24$		$\Delta R32-R12$		$\Delta R32-C$	
		ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF R12	ABS.	IN PER CENT OF C
Heart rate (beats/min.)	32 20	-19.9† —	-36.1 —	-17.9† -17.4	-32.4 -31.7	11.9† 12.5	31.9 33.3	21.2†	56.5	8.7†	17.4	3.8†	6.9
Range of heart rate absolute	32 20	-6.4† —	-65.2 —	-6.1† -6.5	-64.3 -66.4	4.2† 3.9	123.1 118.2	7.1*	215.2	3.2*	44.5	0.6	6.1
Range heart rate in per cent of aver. rate	32 20	-6.6† —	— —	-5.9† -6.5	— —	5.3† 5.0	— —	9.1†	—	4.0†	—	2.5	—
Absol. Q-T (x 100)	32 20	10.3† —	28.8 —	9.3† 9.7	25.9 26.8	-3.8† -4.4	-8.4 -9.6	-6.0†	-13.1	-1.6*	-3.9	3.7†	102.3
Absol. mechan. systole dura- tion (x 100)	32	6.8†	20.9	6.8†	20.9	-2.1†	5.3	—	—	—	—	—	—
K _{Q-T} (x 100)	32 20	-0.5 —	-1.4 —	-0.7 -0.6	-1.9 -1.6	1.8† 1.5	5.0 4.1	2.3†	6.3	0.8	2.1	1.7†	4.5
K _{SYST} (x 100)	32	-2.5†	-7.4	-2.0†	-6.0	2.8†	8.9						

*Statistically significant at 5 per cent level.

†Statistically significant at 1 per cent level.

behind the changes of cycle length. In semistarvation with a lengthening cycle the Q-T interval and the systole duration remained relatively too short, and in rehabilitation with a shortening cycle both intervals remained relatively too long. The validity of the formula for "K" may be questioned, but at least it is useful for description.

In the period from R12 to R32 there was a further decline of the absolute Q-T interval associated with a further increase of the heart rate, but the Q-T interval remained unusually long during the total period of rehabilitation. This is apparent when the values at R32 are compared with the control values, C. At R32, the pulse rate was higher than in the control period C, while the absolute Q-T interval was greater, and not shorter as should be expected. The difference between R32 and C for K_{Q-T} is statistically highly significant. The difference between R32 and C for the heart rate, about four beats, although statistically significant, is so small that all formulas suggested for the relation of the Q-T interval to cycle length would show the same results, since in so narrow a limit the curves of all formulas are practically straight lines. The relative Q-T prolongation is one of the most persistent electrocardiographic changes after semistarvation.

Amplitude Changes.—Tables III and IV show amplitude and axis changes; Table III gives the absolute values and standard deviations, while Table IV gives the absolute and percentage differences and their statistical significance. Values for the QRS complex and T-wave amplitude for Lead III are omitted because the changes in this lead can be inferred from the amplitudes in other leads and the axis as given in Table III. There was a very marked decrease of the P wave, the QRS complex, and the T-wave amplitude in Lead I at S12, while the amplitude of T_2 and Σ_T did not change essentially. The decrease of the QRS amplitude in Lead I is most pronounced, due to a combined effect of QRS axis shift and decrease of QRS amplitude. The decrease of T_1 at S12 is due solely to the right axis shift of the T axis. In the interval from S12 to S24 the amplitudes of P_2 , of the QRS complex, and of T_1 continued to decrease at about the same rate as during the first twelve semistarvation weeks. The amplitude of the T wave (T_2 and Σ_T), which was still unchanged at S12, thereafter declined rapidly so that the percentage decrease of R_2 , Σ_{QRS} , T_2 , and Σ_T was about the same at S24. Changes of Σ_{QRS} and Σ_T could, to a certain extent, be produced by axis changes. Calculation of the manifest potential or the correction factor of Ashman and Byer¹¹ could be used for a closer estimate of the actual voltage changes. However, the changes of the amplitudes are too great to be possibly accounted for by any axis changes. There was unquestionably a very pronounced and statistically highly significant drop of the actual voltage of all deflections of the electrocardiogram at the end of semistarvation.

The time course of the voltage changes in semistarvation was different from the time course of the interval changes; the interval changes had reached their maximum already at S12, while the amplitude and axis changes reached their maximum deviation at S24. It may be concluded that the interval changes and

TABLE III. AMPLITUDES AND AXIS OF THE ELECTROCARDIOGRAM DURING SEMISTARVATION AND REHABILITATION. MEAN VALUES AND STANDARD DEVIATIONS OF THIRTY-TWO AND TWENTY SUBJECTS

FUNCTION	NO. OF SUB- JECTS	CONTROL		S12		S24		R12		R32	
		M	$\pm\sigma$	M	$\pm\sigma$	M	$\pm\sigma$	M	$\pm\sigma$	M	$\pm\sigma$
P wave (mm.) Lead II	32 20	1.01 0.99	0.40	0.68 —	0.40	0.52 0.50	0.34 —	0.81 0.86	0.38 —	— 1.06	— 0.40
R wave (mm.) Lead I	32 20	3.75 3.24	1.89 —	2.10 —	1.05 —	1.45 1.38	0.85 —	2.44 2.04	1.30 —	— 5.57	— 2.43
R wave (mm.) Lead II	32 20	9.91 9.30	4.15 —	8.03 —	2.30 —	6.23 6.08	2.18 —	7.09 6.74	2.45 —	— 8.69	— 2.89
Σ_{QRS}	32 20	23.49 22.60	7.75 —	18.43 —	4.10 —	14.37 14.28	4.00 —	16.65 16.19	4.91 —	— 22.80	— 4.74
T wave (mm.) Lead I	32 20	1.70 1.74	0.78 —	1.14 —	0.51 —	0.46 0.47	0.31 —	1.20 1.11	0.49 —	— 2.90	— 0.91
T wave (mm.) Lead II	32 20	2.73 2.88	1.07 —	2.80 —	1.32 —	1.70 1.83	1.09 —	2.92 2.96	1.00 —	— 3.08	— 1.04
Σ_T (mm.)	32 20	5.59 5.81	2.51 —	5.60 —	2.55 —	3.53 3.79	1.92 —	5.82 5.92	1.99 —	— 6.89	— 1.77
QRS axis°	32 20	68.4 70.4	15.9 —	77.8 —	9.29 —	81.6 82.4	10.02 —	69.8 71.2	2.06 —	— 54.2	— 22.4
T axis°	32 20	47.5 53.4	23.5 —	65.9 —	6.57 —	69.8 72.8	23.9 —	65.2 67.6	9.44 —	— 33.6	— 17.4

the voltage or axis changes are not closely related to one another and may be due to different causes. Also, there are discrepancies in the time course of amplitude decrease between Σ_{QRS} and R_2 on the one hand and Σ_T and T_2 on the other hand. It seems probable, therefore, that the QRS amplitude changes and the T-wave amplitude changes are also due to different causes.

Although in rehabilitation all amplitudes were increased significantly already at R12, the amplitudes of P_2 , R_1 , R_2 , Σ_{QRS} and T_1 were still well below the control values (C), while the T_2 and Σ_T amplitude had already reached the control values. In the interval from R12 to R32 all amplitudes showed further increases which were highly significant except for T_2 . While the major part of the recovery of Σ_{QRS} was completed only in the period from R12 to R32, the major part of the recovery of the T amplitude was completed at R12. While Σ_{QRS} was not significantly different from the control value at R32, Σ_T exceeded the control value by 18.6 per cent, and this difference was statistically significant. This means that discrepancies of the time course between QRS and T changes were observed not only during semistarvation, but also during rehabilitation.

Axis Changes.—Both QRS axis and T axis shifted to the right during semistarvation. This unidirectional shift is of interest, since under many conditions

TABLE IV. AMPLITUDE CHANGES IN THE ELECTROCARDIOGRAM DURING SEMISTARVATION AND REHABILITATION, EXPRESSED AS DIFFERENCES BETWEEN VARIOUS PERIODS, ABSOLUTE AND IN PERCENTAGE OF THE PRECEDING REFERENCE PERIOD (THE VALUES CORRESPOND TO THOSE OF TABLE III)

FUNCTION	NO. OF SUB- JECTS	$\Delta C-S12$		$\Delta C-S24$		$\Delta R12-S24$		$\Delta R32-S24$		$\Delta R32-R12$		$\Delta R32-C$	
		ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF C	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF S24	ABS.	IN PER CENT OF R12	ABS.	IN PER CENT OF C
P wave (mm.) Lead II	32 20	-0.33† —	-32.6 —	-0.49† -0.49	48.5 49.5	0.29† 0.36	55.9 72.0	— 0.56†	— 111.1	— 0.20†	— 23.3	— 0.07	— 7.0
R wave (mm.) Lead I	32 20	-1.65† —	-44.0 —	-2.30† -1.86	-61.4 -57.5	0.99† 0.66	68.4 47.8	— 4.19†	— 306.5	— 3.53†	— 173.2	— 2.33†	— 71.9
R wave (mm.) Lead II	32 20	-1.88† —	-19.0 —	-3.68† -3.22	-37.2 -34.6	0.86† 0.66	13.8 10.9	— 2.61†	— 42.9	— 1.95†	— 28.9	— -0.61	— -6.6
Σ QRS (mm.)	32 20	-5.06† —	-21.6 —	-9.12† -8.32	-38.8 -36.5	2.28† 1.91	15.9 13.4	— 8.52†	— 59.7	— 6.61†	— 40.8	— 0.20	— 8.9
T wave (mm.) Lead I	32 20	-0.56† —	-32.9 —	-1.24† -1.27	-73.0 73.0	0.74† 0.64	160.7 136.0	— 2.43†	— 517.2	— 1.79†	— 161.1	— 1.16†	— 66.7
T wave (mm.) Lead II	32 20	0.07 —	2.5 —	-1.03† -1.05	-37.7 -36.5	1.22† 1.12	71.8 60.8	— 1.25†	— 68.4	— 0.12	— 4.1	— 0.20	— 6.9
ΣT (mm.)	32 20	0.01 —	0.2 —	-2.06† -2.02	-36.9 -34.8	2.30† 2.13	65.2 56.3	— 3.10†	— 81.7	— 0.97*	— 16.4	— 1.08*	— 18.6
QRS-axis°	32 20	9.4† —	— —	13.2† 12.0	— —	-11.8† -11.8†	— —	— -28.2†	— —	— -17.0†	— —	— -16.2	— —
T axis°	32 20	18.4† —	— —	22.3† 19.4	— —	-4.6 -5.2	— —	— -39.2†	— —	— -34.0†	— —	— -19.8†	— —

*Significant at the 5 per cent level.

†Significant at the 1 per cent level.

QRS and T axes change in the opposite direction. The changes of the T axis were greater than the changes of the QRS axis, but both were statistically highly significant. It appears that a change of the direction of repolarization occurred during semistarvation. The axis changes were continuous during this period. There was no significant correlation between QRS-axis and T-axis changes at S24.

In the rehabilitation period, both QRS axis and T axis shifted back to the left. While the QRS axis attained the control values at R12, the T axis was still much closer to the S24 values; in fact, the changes of the T axis ($\Delta R12-S24$) were not significant, in contrast to the highly significant changes of the QRS axis.

In the period from R12 to R32, the QRS axis, and to a greater extent the T axis, continued to shift toward left. At R32, the QRS axis and especially the T axis were shifted to the left as compared to the control values and these differences were statistically highly significant.

Fig. 1 shows the changes during starvation and rehabilitation of a few fundamental functions: average heart rate and range of variability of heart rate, R_2 and T_2 amplitudes, and QRS and T axes. For the periods C to R12, the values of the total group of thirty-two subjects were taken, and for the period R32 the values of the twenty subjects were used, with a correction for the absolute differences of the control values between both groups. The discrepancies in the time course between the heart rate changes and the amplitude changes are obvious.

Fig. 2 shows the typical sinus bradycardia, right axis shift, and decrease of the P, QRS, and T amplitudes during starvation on one of our subjects. The changes are regressive at R12. While the electrocardiograms of all subjects (except one with a left axis shift bordering on left ventricular preponderance) were within normal limits before the experiment started, the majority (75 per cent) would have to be classified as abnormal at S24 because of low voltage of the QRS complex and T waves.

Effect of the Caloric Level in the Rehabilitation Period.—In the preceding analysis of our results, the effect of rehabilitation was discussed without differentiation of the four caloric groups; these were spaced in intervals of 400 calories and designated in increasing order as Z, L, G, and T. As has been shown, the recovery of most electrocardiographic functions was far from complete at R12; in fact, the recovery of many functions was only slight, although statistically significant. Therefore, no clear-cut differentiation of the different caloric groups could be expected at that time, while later, after the twelfth week, the diet was no longer controlled. However, a complete statistical analysis was made, and a statistically significant differentiation of caloric groups was found for the following items: duration of mechanical systole, K_{Q-T} , R wave in Leads I and II, Σ_{QRS} , T wave in Leads I and II, Σ_T , and T axis.

The differentiation was significant only in the extreme groups, either Group Z (for instance, mechanical systole duration) or Group T (for instance, R_1) was

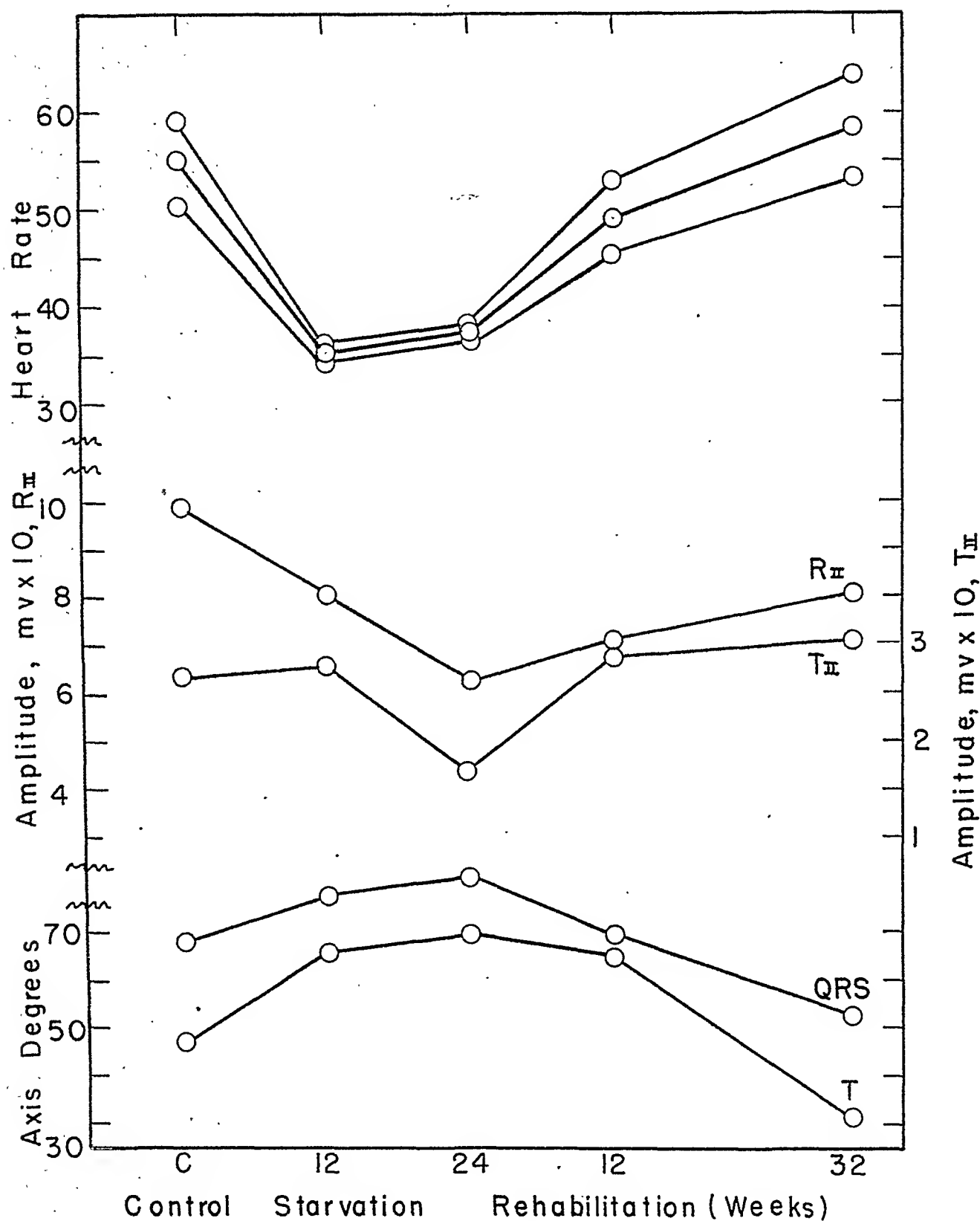


Fig. 1.—Changes of heart rate, R_2 amplitude, T_2 amplitude, QRS axis, and T axis during starvation and rehabilitation. The upper part of the graph shows the changes of the average heart rate (middle curve) and the variability of the range of the heart rate, calculated from the longest and shortest R-R interval (lower and upper curve). The middle part of the graph shows the amplitude changes in $mv. \times 10$ of the R wave and T wave in Lead II. The lower part of the graph shows the changes of the QRS axis and T axis.

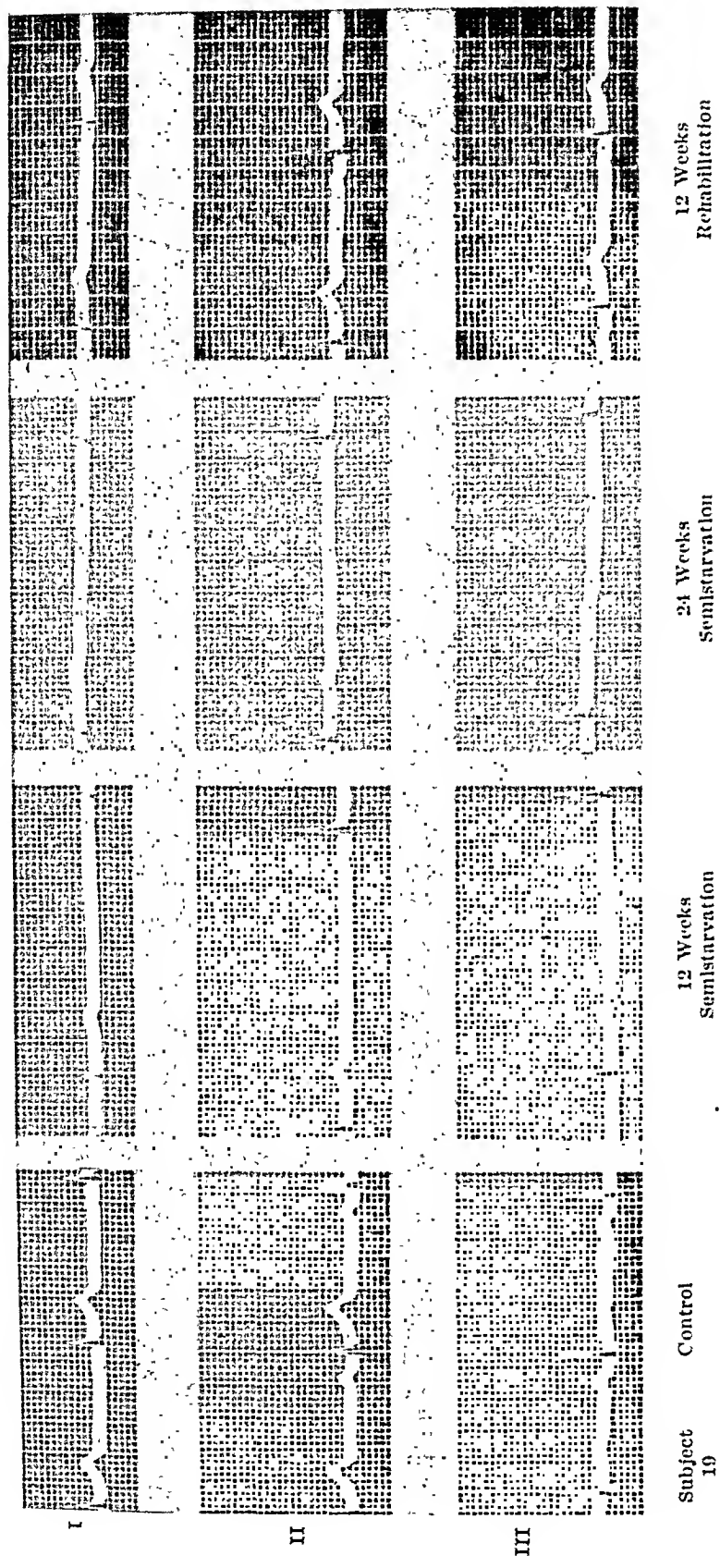


Fig. 2.—Electrocardiograms of a typical subject during control, semistarvation, and after twelve weeks of rehabilitation.

significantly different from the other three caloric groups, or the extreme groups (T versus Z) were significantly different, or the combined groups G+T versus L+Z were significantly different.

There was no significant difference of any electrocardiographic function in regard to high and low protein intake or high and low vitamin intake. It seems that the duration of mechanical systole and the R_1 amplitude might be especially useful for differentiation of caloric groups in rehabilitation.

The Effect of Maximum Inspiration.—One of the most pronounced changes during semistarvation is the sinus bradycardia. While the slowing of the heart rate may be regarded as an adaptation to the decreased metabolic rate, the underlying mechanism was not clear when the experiment was started. The effect of a maximal voluntary inspiration was used as a possible approach to study the pulse rate regulation. In the early phase of the maximal inspiration, the acceleration of the heart rate, probably due to sympathetic stimulation, was observed in all subjects, while a retardation below the resting pulse rate in the late phase of maximal inspiration, obviously a vagus effect, was present only in eighteen subjects. The analysis of the late effects of maximal inspiration was made only in those eighteen subjects who showed a definite vagus effect; no change of vagus stimulation during semistarvation could be expected if such an effect were absent in the control period (C).

Table V shows the effect of the early and the late phase of maximal inspiration on the heart rate, on K_{Q-T} , and K_{SYST} . The values show the changes produced by the maximal inspiration, as compared with the values at rest. The

TABLE V. RESPONSE TO MAXIMUM INSPIRATION (MEAN VALUES, DIFFERENCES, AND STATISTICAL SIGNIFICANCE)

FUNCTION	NO. OF SUBJECTS	C	S24	R12	Δ S24-C	Δ R12-24	PHASE OF MAX. INSPIR.
Heart rate	30	21	14.5	16.8	-6.5†		Early
Heart rate	32		14.5	16.5		2.0	Early
Heart rate	18	-7.1	-1.9	-3.7	5.2†	-1.8*	Late
Range of heart rate, difference rest-max. inspir.	30 32	24.7	15.3 15.3	18.4 19.4	-9.4†	4.1	Total duration
K_{Q-T} (x 100)	30	73.5	63.8	55.8	-9.7	-8.0	Early
K_{Q-T} (x 100)	31	-26.2	-14.5	-35.3	+11.7*	-20.8†	Late
K_{SYST} (x100)	28	-26.9	-15.6	-32.2	+11.3*	-16.6†	Late
Mech. syst. dur. (x 100)	28	-1.53	-0.86	-1.25	+0.67*	- 0.39	Late

*Significant at the 5 per cent level.

†Significant at the 1 per cent level.

initial acceleration, as well as the late retardation effect, was much less pronounced at S24 as compared to C, and this decrease was statistically highly significant. During twelve weeks of rehabilitation, there was no significant change in the initial acceleration, while the retardation effect became more pronounced again, so that the difference of the response $\Delta R12-S24$ was significant at the 5 per cent level. However, the retardation response was still definitely less than it had been before starvation (C).

The range of heart rate under the influence of maximum inspiration was calculated as the difference between the shortest and longest cycle, and was compared with the variability range during rest (Table I). Since both initial acceleration and late retardation decreased in semistarvation, the range of the heart rate showed a corresponding decrease at S24; the recovery was far from complete at R12.

It is known that the adaptation of the Q-T interval to rapid changes of the cycle length is incomplete, so that pronounced changes of K_{Q-T} occur. However, this coefficient is still useful for an analysis of a possible change in the mechanism of Q-T cycle adaptation. In calculating the effect of the late phase of respiration, the values of all subjects were used.

The increase of K_{Q-T} in the early phase of maximum inspiration, above the resting values of Table I, did not change significantly during semistarvation and rehabilitation. The decrease of K_{Q-T} and K_{STBT} in the late phase of maximal inspiration, indicating a lag of adaptation to the increasing cycle length, was much smaller at S24. This trend was reversed again in rehabilitation, even overshooting the control values (C) at R12. The changes were statistically significant. The mechanical systole could not be determined at the early phase of maximal inspiration because of the interference of the noise produced by the inspiration. The fact that the values at R12 overshoot the control values (C), while the recovery of the heart rate was still far from complete at that time, suggests that there is a direct effect of semistarvation on the response of Q-T and mechanical systole to maximum inspiration, which is independent, to a certain extent, of the response of the heart rate. This is borne out by analysis of the absolute systole duration. The response of the whole group was significantly less at S24, as shown in Table V. The total group was divided according to the presence of a vagus retardation effect on the heart rate in the late phase of maximal inspiration. The mean values of the mechanical systole for fifteen subjects with retardation were -1.53 , -0.93 , and -1.33 for the periods C, S24, and R12, respectively. The mean values for thirteen subjects without retardation of the heart rate were -1.53 , -0.73 , and -0.14 , respectively. There were no significant differences between the group with retardation and the group without retardation.

Occasional Observations.—Some interesting occasional observations were made in a few subjects. In Subject 102 (first subject of Fig. 3), the P wave became slightly negative during the late phase of maximal inspiration (indicated by the

signal) with shortening of the P-R interval after four weeks of semistarvation. Later, the P wave disappeared entirely at the end of maximal inspiration, and this phenomenon remained the same also during twelve weeks of rehabilitation.

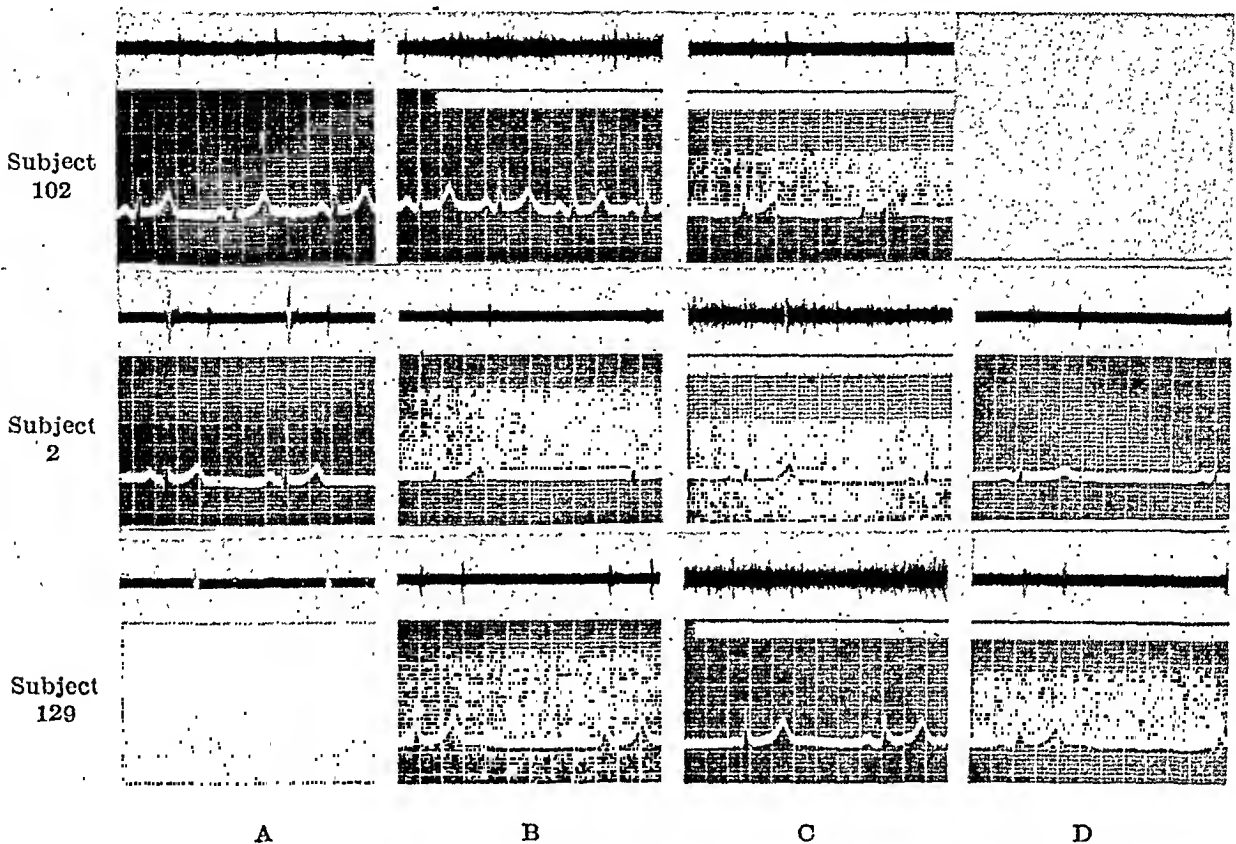


Fig. 3.—Subject 102, fifth week of starvation. A = Lead II, before maximum inspiration. B = Lead II, early phase of maximum inspiration. Increased heart rate, no change of P wave. C = Lead II, late phase of maximum inspiration: nodal rhythm.

This phenomenon remained the same during semistarvation and rehabilitation.

Subject 2. A = Control period; Lead II at rest. Sinus rhythm. B = Lead II, thirteenth week of starvation, at rest before maximum inspiration. Nodal rhythm. C = Same E.C.G., same lead, during late phase of maximum inspiration. A P wave has appeared, indicating re-establishment of sinus rhythm. D = Sinus rhythm is still present in the subsequently taken Lead III.

Subject 129. A = Control period, Lead II; normal sinus rhythm. B = Fifth week of starvation, Lead II, before maximum inspiration. Nodal rhythm. C = Already, in the early phase of maximum inspiration, a P wave appears which is present only during the maximum inspiration. D = Late phase of maximum inspiration. The P-R interval in the last beat is shortened to 0.1 second; in the subsequent beats no P-wave is present.

In Subject 2, just the opposite phenomenon occurred. Beginning at S13, the sinus rhythm was replaced by nodal rhythm (second and third subjects of Fig. 3), but maximal respiration produced a transitory restoration of the sinus rhythm. In Lead III, taken after Lead II, the sinus rhythm was still present. Also, in Subject 129, the normal sinus rhythm (third subject, Fig. 3,A) was replaced by a nodal rhythm (third subject, Fig. 3,B) as early as S5. In the early phase of maximal respiration, a small P wave with a short P-R interval (0.09 second) appears in the first beat (third subject, Fig. 3,C) while in the second beat the P wave is of about normal (prestarvation) amplitude with a P-R interval of 0.19 second. In the late phase of maximal inspiration, the P-wave amplitude and P-R interval decrease again; the P-R interval in the first beat of Fig. 3 (third

subject, D) is 0.16 second, in the second beat 0.10 second, indicating nodal rhythm again. Although the effect of maximum inspiration is similar in both subjects, the sinus rhythm is restored for a much shorter time in Subject 129, in fact, it is restricted to the duration of the maximum inspiration. These were the only subjects in whom semistarvation produced a nodal rhythm.

DISCUSSION

Relation to Previous Records.—Our results are confirmatory to the general observations of decreased QRS and T-wave amplitude in famine areas, but the latter have only the character of occasional observations in patients, while in our experiments quantitative relationships were obtained under controlled conditions.

Our results disagree with the reports of Cardozo and Eggink⁴ and of Ellis⁵ that the Q-T interval is lengthened in relation to the cycle length. The only explanation we are able to offer for the discrepancy is the possibility that these authors happened to investigate another (and generally more advanced) phase of semistarvation.

Amplitude Changes.—The decrease of the QRS and T-wave amplitudes is probably the most significant change of the electrocardiogram in starvation. It may be due to the following causes:

1. *Decrease of Heart Size:* The decrease of the amplitudes was accompanied by a very marked decrease of the heart size as determined by teleroentgenograms and roentgenkymograms. These results are presented elsewhere¹; it may be mentioned that there is also good evidence from autopsy material that the heart weight decreases in semistarvation much in proportion to the loss of body weight.¹²⁻¹⁴ Since in the hypertrophic heart the QRS amplitude is, as a rule, increased, it might seem logical to assume that a decrease in an atrophic heart would be explained on this basis alone. However, this assumption should not be made without reservations, since secondary changes in the hypertrophic heart, which are absent in the atrophic heart, might be contributory.

2. *Myocardial Degeneration:* There is evidence of widespread degenerative histologic changes in the hearts of starved animals¹⁵⁻¹⁷ which has been confirmed recently by Pollack¹⁸ in human autopsy material.

3. *Decreased Metabolic Rate:* Although there is no outright correlation between QRS amplitude and the basal metabolic rate, both QRS and T amplitudes are usually decreased in hypothyroidism and have a tendency to be increased in hyperthyroidism. The average basal metabolic rate of our group decreased 37 per cent during semistarvation, and at R12 was still only 82 per cent of the prestarvation control.

4. *Fluid Accumulation in Chest or Pericardium:* Although twenty-eight out of thirty-two of our subjects showed clinical edema during semistarvation there was no evidence to indicate an accumulation of fluid in the chest or pericardium.

Axis Changes.—The right axis shift of the QRS complex was probably due to positional changes; a smaller heart tends to assume a more vertical position. A right axis shift of the anatomic axis was obvious in the x-ray studies.¹ However, there was no exact correlation between the right axis shift of the anatomic axis and the QRS axis; this discrepancy might be due to the fact that the x-ray studies were made in the standing position, while the electrocardiograms were taken in the supine position.

It is also possible that the right axis shift of the QRS axis is due to a relative right ventricular preponderance or to a change in the pathway of excitation. A relative right ventricular preponderance could be produced by a greater degree of atrophy in the left ventricle; there are no data available to support or to contradict such assumption. In this connection, it is interesting that in Tur's material right axis shift was more common in the advanced cases than it was in the milder cases. The main reason for the overshooting of the left axis shift in rehabilitation is probably mechanical: all men were fatter, particularly in the abdominal region, at R32 than they were at C; the increased volume of the abdominal organs would explain a position of the axis farther to the left.

Heart Rate.—The slow heart rate in semistarvation is referable to a sinus bradycardia in most cases, but our material shows that in exceptional cases nodal rhythm occurs. The occurrence of nodal rhythm would be compatible with the assumption that the slow heart rate in semistarvation is due to increased vagus tone. Schiff¹⁹ reported that atropine (0.5 to 0.75 mg.) promptly abolished starvation bradycardia for a transitory period, but Schittenhelm and Schlecht²⁰ found no effect whatever with 1.0 mg. of atropine. We found not only the late vagus effect, but also the early sympathetic acceleration of the heart rate to be decreased in maximum inspiration. Since both vagus and sympathetic response are diminished, the slow heart rate may be due to both increased vagus tone and loss of sympathetic tone. This would agree with Hoesslin's²¹ observations of the absence of emotional pulse rate changes in semistarvation and with our findings of the decreased range of variability.

Jordan's²² observation that the initial digitalis retardation of the heart rate fails to appear in starving dogs is an interesting corroboration of our results. Statkewitsch's²³ findings of extensive pathologic changes in the cardiac ganglia of rabbits in advanced inanition might be regarded as histologic evidence for the loss of vegetative regulation which would only be very slowly reversed in rehabilitation.

Significance of Our Results for Heart Pathology in Malnutrition.—Except for the beriberi heart, the condition of the heart in states of malnutrition has found little attention in clinical medicine. In several recent textbooks of cardiology,²⁴⁻²⁹ no mention is made of the importance of the nutritional state for cardiac pathology. Vaquez²⁰ recognized the theoretical importance of nutritional effects on the condition of the myocardium, but he was inclined to believe that the effect is insignificant. Although in general there is little correlation between electrocardiographic findings and the functional state of the heart,

the occurrence of significant changes in most electrocardiographic items during semistarvation cannot be ignored. It seems safe to conclude that they indicate myocardial changes. The implications of the present results would be that prolonged semistarvation produces a deterioration of the state of the myocardium, which might be functionally compensated for a time. However, the compensation might break down under conditions of additional stress. In the present study such stress conditions were excluded, but they might well arise under less well-protected conditions. In connection with this, it is interesting to note that one of our subjects suddenly became decompensated in the early rehabilitation period; the heart became enlarged and the venous pressure rose abruptly. Treatment with bed rest, reduced food intake, and diuretics restored the patient within one week. The reason the decompensation appeared in the rehabilitation period might be the increased circulatory load due to sharply increased food ingestion and greater activity.

SUMMARY

1. In thirty-two normal subjects, electrocardiograms were taken at regular intervals during a control period of three months, during a semistarvation period of six months in which a 24 per cent weight loss was produced, and during a controlled rehabilitation period of twelve weeks. In twenty subjects, electrocardiograms were taken also after thirty-two weeks of rehabilitation, the last twenty weeks being on a freely chosen diet.

2. During semistarvation, statistically highly significant changes occurred in most electrocardiographic items, and the electrocardiograms became clinically abnormal in the majority of subjects.

3. There was pronounced slowing of the heart rate, and its variability range decreased both relatively and absolutely so that the heart rate was more regular in semistarvation. These changes reached their maximum at the twelfth week of semistarvation, and recovered slowly during rehabilitation.

4. Q-T interval and mechanical systole duration increased during semistarvation and shortened again during rehabilitation, but these changes lagged behind the simultaneous changes of the cycle length in both directions, so that K_{Q-T} and K_{SYST} changed accordingly.

5. The amplitudes of all deflections (P wave, QRS complex, and T wave) decreased continuously and very considerably during semistarvation and recovered slowly during rehabilitation.

6. During semistarvation, there was a marked right axis shift of the QRS axis and even more so of the T axis, so that the angle between both axes was diminished. During rehabilitation, both QRS axis and T axis moved to the left, overshooting the original prestarvation position at the thirty-second week of semistarvation.

7. Most electrocardiographic items were only partially recovered during twelve weeks of rehabilitation, but were back to the control values within thirty-

two weeks, several functions (heart rate, R_1 , Σ_T , QRS axis, T axis) overshooting the control values subsequently.

8. There was a discrepancy in the time course of changes between interval and amplitude changes, and between QRS complex and T-wave changes.

9. There was no correlation between QRS axis changes and anatomic axis changes, or between QRS axis and T axis, although all changed in the same direction.

10. A statistically significant differentiation of the groups receiving different caloric levels during rehabilitation was obtained in the following items: systole duration, K_{QT} , R_1 , R_2 , Σ_{QRS} , T_1 , T_2 , Σ_T , and T axis.

11. Before semistarvation, voluntary maximal inspiration produced an initial acceleration of the heart rate in all subjects, which was followed by a late retardation in eighteen subjects.

12. During semistarvation, the effect of maximal inspiration was diminished in respect to both initial acceleration and late retardation. During twelve weeks of rehabilitation, only the late retardation was restored.

13. The decrease of K_{QT} and K_{SYST} in the late phase of maximal inspiration was significantly less pronounced at the end of semistarvation, and this effect was, to a certain degree, independent of the changes in the heart rate.

14. While the slow heart rate in semistarvation, as a rule, was due to sinus bradycardia, in two subjects nodal rhythm was observed; this was temporarily restored to sinus rhythm during maximum voluntary inspiration.

ACKNOWLEDGMENT

This work would not have been possible without the loyal cooperation of the volunteers from Civilian Public Service who acted as subjects, and others who gave assistance. Mr. Arthur Butler made the detailed measurements of the electrocardiograms. Dr. Howard Alexander and Mr. Richard Seymour supervised the statistical work. Most of the electrocardiograms were taken by Miss Angie Mae Sturgeon.

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RESPONSE OF PERSONS WITH AND WITHOUT INTRAVASCULAR THROMBOSIS TO A HEPARIN TOLERANCE TEST*

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IN NOVEMBER, 1942, de Takats and Gilbert¹ presented a paper on use of the response to heparin as a test of the clotting mechanism of the blood. In July, 1943, de Takats² published further data on this subject and gave the name "heparin tolerance" to the test. Without detracting from the possible value and importance of this approach to the study of blood coagulability in health and disease, we wish to point out that the exact technique used by these authors appears to be open to certain criticisms. First, a relatively small amount of heparin was used, thus perhaps limiting the range of response to the anticoagulant. Second, since capillary blood was tested, possibly the presence of variable amounts of tissue thromboplastin limited the accuracy of comparable determinations of coagulation time. Third, the coagulation test used was that of breaking blood-filled capillary tubes, which is not considered an accurate standard coagulation test. Fourth, the differences in the time given for normal and abnormal reactions were small and possibly within the limits of probable error of the method.

PURPOSE OF STUDY

Because of the tremendous interest during the last few years in the factors responsible for thrombosis and embolism, the work reported in abridged form herein was undertaken to substantiate de Takats and Gilbert's major premise by utilization of a slightly different technique. After the beginning of this work and before its completion, de Takats and co-workers³⁻⁵ published other papers on the effect of administering various drugs and of nervous regulation on the clotting mechanism as indicated by the results of the heparin tolerance test. Earlier, Macht⁶ had pointed out the effect of administration of certain drugs on the response to injection of heparin. Since our primary aim was to measure the response to the heparin tolerance test in normal individuals and in those with conditions associated with thrombosis, we have not attempted to investigate the numerous implications suggested by the papers to which we have just referred.

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*Abridgment of thesis submitted by Dr. Hagedorn to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

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METHODS

We decided to administer intravenously an arbitrary dose of 25 mg. of heparin in 2.5 c.c. of liquid and to study the effect on the coagulation time in different individuals. The coagulation time was determined by a slight modification of the method of Lee and White⁷; that is, by the inversion, every thirty seconds, of a 10 by 75 mm. Wassermann-type glass tube containing 1 c.c. of blood withdrawn from a vein of the arm. The coagulation time was determined before the injection of the heparin intravenously and at intervals of ten, twenty, thirty, forty, and sometimes fifty, sixty, and ninety minutes after injection. All tests of the coagulation time were done at the usual temperature of the hospital room.

The fifty control subjects were adult men and women between the ages of 18 and 62 years and were all apparently healthy. For the most part, the seventy patients were those suffering from peripheral vascular disease with old or recent intravascular thrombosis. For convenience, the patients were separated into five categories: (1) those with thromboangiitis obliterans; (2) those with arteriosclerosis obliterans; (3) those with thrombophlebitis, old and recent; (4) those with conditions associated with types of thrombosis other than those of the preceding three categories; and (5) those suffering from miscellaneous diseases

TABLE I. COAGULATION TIME, IN MINUTES, OF THE BLOOD OF THE FIRST ELEVEN CONTROL SUBJECTS BEFORE AND AT STATED INTERVALS AFTER THE INTRAVENOUS INJECTION OF 25 MG. OF HEPARIN

SUBJECT	BEFORE INJECTION	MINUTES AFTER INJECTION OF HEPARIN						
		10*	20	30	40	50	60	90
1	8½	54½	52	36	26		26	18
2	7½	62	37	20	9			
3	6½	94	24½	20½	18½			
4	4½	62	38½		15		13½	
5	6½	59	15½	9	8½			
6	6½	64	50	20	14	8	7½	
7	7	74	50	20	18	12	8	
8	7	58	46	30	18	11	9	
9	6½	54½	47	24	12	9½		
10	7	90	50	55	20		18	
11	8	110	24½	20	9½			

*Note the maximal response at ten minutes after the intravenous injection of 25 mg. of heparin in 2.5 c.c. of solution.

not associated with known thrombosis. In the fourth category were two patients with simple arterial thrombosis, both of whom made no response to the intravenous injection of heparin, and three patients with postoperative pulmonary infarction, two of whom gave no response and one of whom gave a normal response to administration of heparin.

After heparin tolerance curves had been determined on eleven normal subjects and thirty-seven patients, it was obvious that the maximal response to heparin observed at any of the ten-minute intervals was the one which occurred ten minutes after intravenous injection (Table I). In all subsequent tests, therefore, the coagulation time was determined only before (control) and ten minutes after the intravenous injection of heparin. Thus, only two venepunctures on each subject were necessary instead of the five or six venepunctures previously required, a definite simplification of the procedure.

De Takats and co-workers classified the responses of the blood of different individuals to the intravenous injection of heparin into four groups as follows: normal, hyperactive, hypoactive, and no response. We have classified our results similarly (Fig. 1). If the coagulation time of the sample of blood withdrawn ten minutes after the injection of 25 mg. of heparin was less than ten minutes, the result of the test was considered as indicating no response to heparin; if the coagulation time was ten to forty minutes, the response was considered hypoactive; if it was forty to ninety minutes, the response was considered normal; and if it was more than ninety minutes, the response was considered hyperactive.

RESULTS

The coagulation time of the blood of three normal persons determined before and after the intravenous injection of 25 mg. of heparin did not vary significantly from day to day (Table II). Similar results were obtained in the study

TABLE II. COAGULATION TIME, IN MINUTES, OF THE BLOOD OF THREE NORMAL SUBJECTS DETERMINED ON DIFFERENT DAYS BEFORE AND TEN MINUTES AFTER THE INTRAVENOUS INJECTION OF 25 MG. OF HEPARIN

SUBJECT	FEB. 22, 1945		MARCH 5, 1945		MARCH 9, 1945		APRIL 1, 1945		APRIL 11, 1945	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1	4½	56	6½	63	7½	54	5	60	5½	64
2	5½	51	6	59			5	48	5½	64
3	7	48	7	44	7	52			7	57

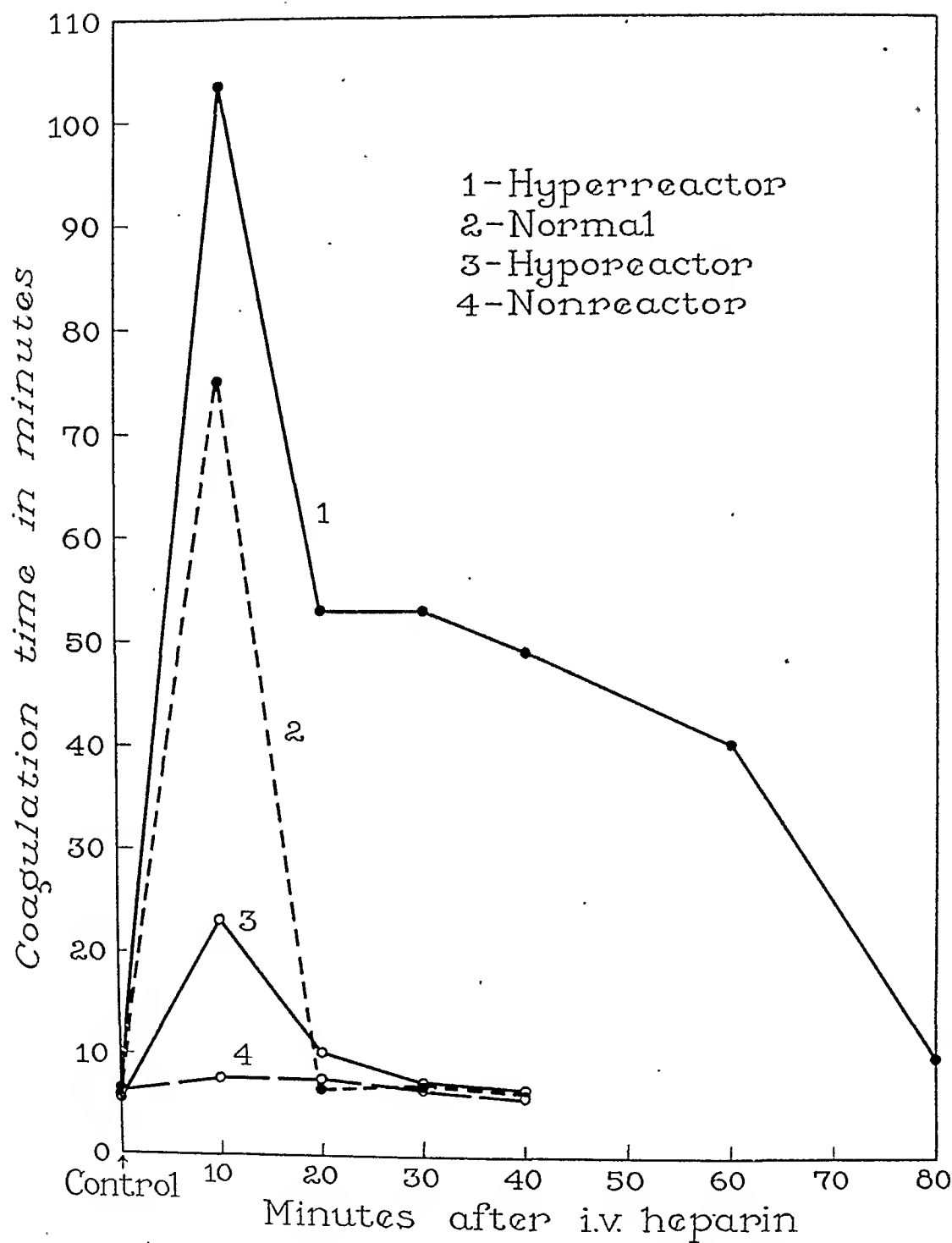


Fig. 1.—Heparin tolerance curves showing the four types of responses obtained.

of nine patients. The results were consistent. Results on one of these patients are shown in Fig. 2. An individual who gave no response to heparin on one day also gave no response to heparin when the test was repeated on another day; an individual who gave a hypoactive response on one day also gave a hypoactive response when the test was repeated a few days later. In contrast, the response to the heparin tolerance test varied considerably among different persons who were suffering from the same disease (Fig. 3).

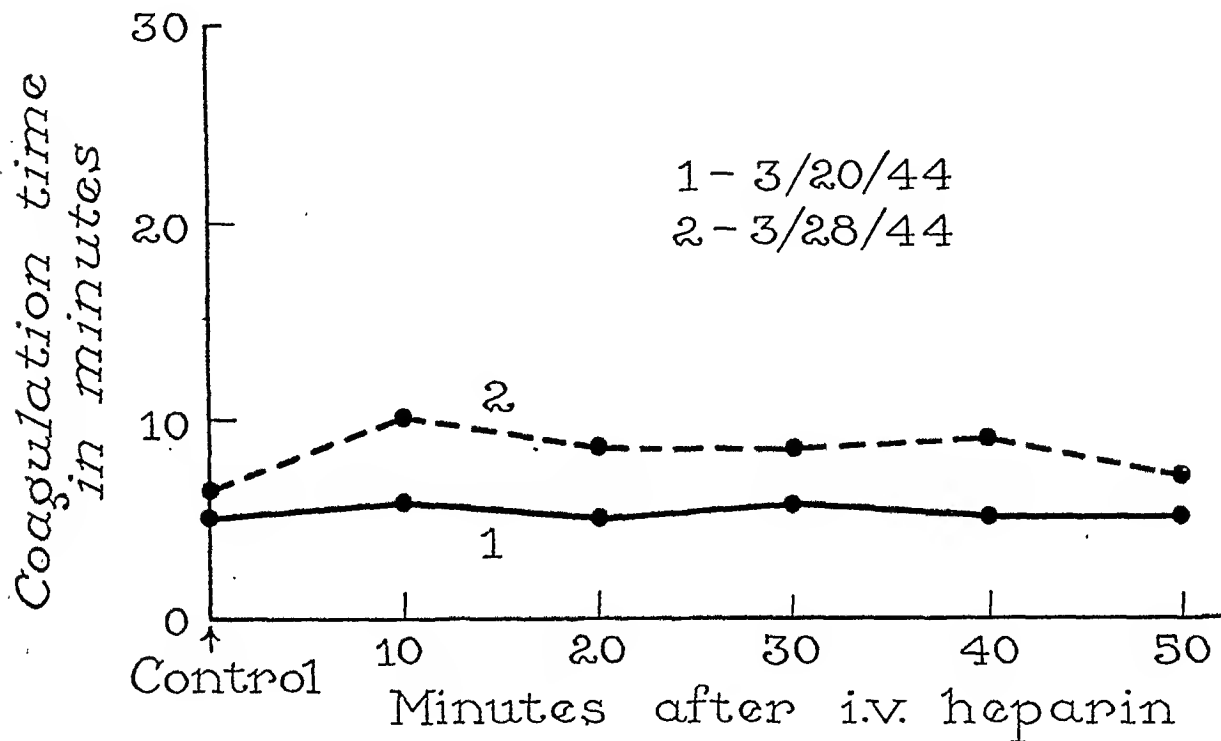


Fig. 2.—Thromboangiitis obliterans: heparin tolerance curves for the same patient on different days.

Two patients to whom heparin was given intravenously experienced mild hypersensitivity to the drug. Neither gave a hyperactive response in terms of the classification of de Takats and co-workers. The first was a patient with chronic pernio whose sensitivity was manifested by a generalized erythema, feeling of giddiness and suffocation, dyspnea, tachycardia, sudden cough, and borborygmus. He had a sensation of coldness of the hands and feet. The manifestations of hypersensitivity lasted less than ten minutes. The heparin tolerance test was carried out as usual; the response with regard to coagulation time was normal. The second patient had chronic rheumatic endocarditis with mitral stenosis, auricular fibrillation, and an acute occlusion of the right brachial artery. This patient's hypersensitivity was manifested by mild pain in the middle part of the back and a "funny feeling." There were no objective signs. These manifestations lasted only three or four minutes. This patient made no response to the injection of heparin in so far as the coagulation time was concerned.

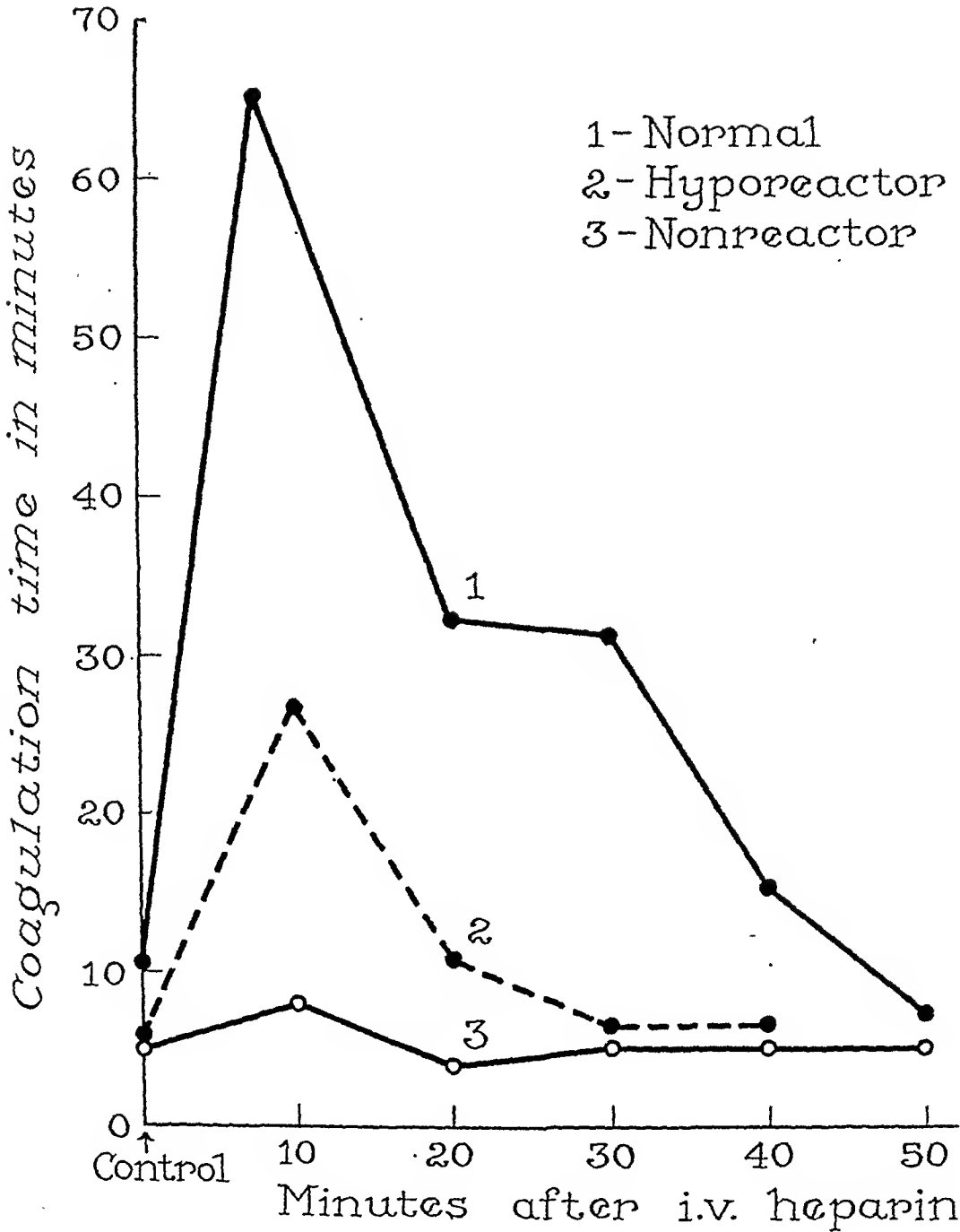


Fig. 3.—Arteriosclerosis obliterans: heparin tolerance curves showing responses in different patients with arterial thrombosis.

The comparative results of our study of the heparin tolerance test in fifty control subjects and in seventy patients with and without evidence of intravascular thrombosis are shown in Table III.

TABLE III. SUMMARY OF THE RESULTS OF A STUDY OF THE HEPARIN TOLERANCE TEST IN SIXTY-ONE PATIENTS WITH EVIDENCE OF INTRAVASCULAR THROMBOSIS, IN NINE PATIENTS WITHOUT EVIDENCE OF INTRAVASCULAR THROMBOSIS, AND IN FIFTY NORMAL SUBJECTS

	TOTAL TESTED	HYPER-REACTORS		NORMAL REACTORS		HYPO-REACTORS		NON-REACTORS	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Patients with thromboangiitis obliterans	22	0		5	23	6	27	11	50
Arteriosclerosis obliterans	18	0		7	39	8	44	3	17
Thrombophlebitis (old and recent)	11	0		5	46	3	27	3	27
Other conditions associated with thrombosis	10	0		2	20	1	10	7	70
Patients with evidence of intravascular thrombosis—total	61	0		19	31	18	30	24	39
Patients without evidence of intravascular thrombosis	9	1	11	5	56	3	33	0	
Normal subjects	50	2	4	47	94	1	2	0	
Patients without evidence of intravascular thrombosis and normal subjects combined	59	3	5	52	88	4	7	0	

COMMENT

We cannot say whether the heparin tolerance test as applied by us can be used to determine the presence or absence of a tendency to intravascular thrombosis, but we believe there is significance in the relatively high incidence of nonreactors and hyporeactors among the patients who had intravascular thrombosis. However, further study of a larger series of cases of thrombosis of various type is indicated. Since the procedure for doing the test is time consuming, a simplification of the method would be desirable.

As previously stated, all coagulation tests were done at the ordinary temperature of the hospital room. They were all made by the same individual who used the same technique and the same set of equipment each time. Therefore, we believe that the results obtained are comparable. We admit that more accurate standardization is desirable⁸⁻¹⁰ but often not practicable.

SUMMARY

The coagulation time of 1 c.c. of venous blood placed in a 10 by 75 mm. Wassermann-type glass tube and inverted every thirty seconds has been obtained on fifty control subjects and seventy patients before and after the intravenous injection of 25 mg. of heparin in 2.5 c.c. of liquid.

The results of the determinations of coagulation time on samples of venous blood withdrawn at ten-minute intervals for variable periods indicated that the maximal response to the intravenous injection of heparin occurred ten minutes after injection.

Of the individuals without evidence of intravascular thrombosis, including the control subjects, 5 per cent were hyper-reactors; 88 per cent, normal reactors; 7 per cent hyporeactors, and none were nonreactors.

Of the individuals with evidence of intravascular thrombosis (categories 1 to 4 in Table III), none were hyper-reactors, 31 per cent were normal reactors, 30 per cent were hyporeactors and 39 per cent were nonreactors.

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HEREDITARY DISTURBANCE OF CHOLESTEROL METABOLISM: A FACTOR IN THE GENESIS OF ATHEROSCLEROSIS

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THE high incidence of coronary atherosclerosis and cardiac infarction among patients with hereditary xanthomatosis is well known. We have recently reported on the relative frequency of hypercholesterolemia, xanthoma tuberosum and tendinosum, arcus senilis, xanthelasma, and coronary artery disease, and have studied sixty-four individuals with this metabolic disorder.¹ Xanthoma families are by no means as rare as was once believed. We have pointed out that in many members of these families the only manifestation of the disease is a high level of serum cholesterol. In several instances, such individuals have subsequently sustained cardiac infarction while under observation.

In some xanthoma families, relatively young persons may be found who exhibit arcus senilis in association with elevated serum cholesterol. Klatskin² reported two such young members in one family and we have made similar observations.³ We have also found young adults with coronary atherosclerosis who are not members of a xanthoma family, but who, nonetheless, present arcus senilis and elevated serum cholesterol. The not infrequent appearance in the same individual of these three pathologic states, arcus senilis, coronary atherosclerosis, and elevated serum cholesterol, suggests that they are more than coincidental.

A clinical correlation between arteriosclerosis and altered cholesterol metabolism has been attempted by several investigators. The first reliable investigation was that of Mjassnikow⁴ who, in 1925, showed that among sixteen patients with atherosclerosis, twelve of whom had angina pectoris, the serum cholesterol level was elevated in every one. Later, Andes and associates⁵ found no difference between the cholesterol values of arteriosclerotic patients and normal individuals. However, it is clear that they were not dealing with atherosclerosis, since their criteria were based on palpation of the radial arteries and on evaluation of the condition of the dorsalis pedis vessels. The pathologic process involving these muscular arteries of the extremities is a medial sclerosis and not an intimal atheromatosis. Elliot and Nuzum⁶ investigated blood cholesterol values in patients with hypertension and arteriosclerosis and found no correlation between

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the level of this blood lipid and the disorders studied. Their criteria also failed to differentiate between types of arteriosclerosis. Soon thereafter, Davis and co-workers⁷ reported that among fifty-nine patients with proved angina pectoris the levels of cholesterol, total and free, lipid phosphorus, and fatty acids were higher than in a comparable group of control subjects. The ages of their patients ranged from 38 to 69 years. More recently, Steiner and Domanski⁸ selected fifteen patients with proved coronary atherosclerosis whose ages ranged from 42 to 72 years and studied their blood cholesterol levels at varying intervals for as long as two years. This carefully conducted research revealed that the patients with coronary artery disease had much higher average serum cholesterol levels than similarly aged normal persons studied over the same period. They found an average serum cholesterol of 355 mg. per 100 c.c. in the group with coronary atherosclerosis and an average of 255 mg. per 100 c.c. in the control group. They also pointed out that, among patients with coronary artery disease, fluctuations in serum cholesterol levels from month to month were much greater than in normal persons, who maintain a relatively constant level through the years. This observation is of special importance and should be kept in mind when interpreting the significance of a "high normal" or "slightly elevated" cholesterol value in a patient with coronary atherosclerosis. Herrmann⁹ found a mean serum cholesterol of 254 mg. per 100 c.c. among 120 patients diagnosed as having atheromatous heart disease with coronary thrombosis, mitral insufficiency, or angina pectoris. In a control group of fifty individuals, the mean serum cholesterol was 193 mg. per 100 cubic centimeters. Lerman and White¹⁰ studied twenty-eight young patients with coronary artery disease and found that twenty-two of them had serum cholesterol values above 250 mg. per 100 cubic centimeters.

Most of these investigators did not confine their observations to younger individuals, nor did any of them study the incidence of hypercholesterolemia among the members of the patients' families. Since altered cholesterol metabolism seems to be the underlying disturbance predisposing to coronary artery disease in young members of families in which there are multiple cases of xanthomatosis, we thought it profitable to study the serum cholesterol levels and search for those stigmata that occur frequently in the presence of hypercholesterolemia in a group of relatively young patients with uncomplicated coronary atherosclerosis and in their siblings. It might be that xanthoma families represent only the extremes of disturbed cholesterol metabolism and that many patients with apparently uncomplicated coronary artery disease might fall into a similar pattern. If this were true, it might help to explain the familial occurrence of coronary artery disease and also give added significance to disturbed cholesterol metabolism in the etiology of coronary atherosclerosis.

If hypercholesterolemia occurs with some frequency in families, one or more of whose members have coronary atherosclerosis, it would seem probable that in these families a disturbance of cholesterol metabolism is the basic hereditary disorder predisposing to atherosclerosis.

METHODS AND MATERIAL

The patients were seen in the office practice of one of us (E.P.B.) and consisted of unselected, consecutive cardiac patients with proved coronary artery disease whose symptoms *began* under the age of 50 years. The vast majority were Jewish. Only patients with symptoms of coronary artery disease and electrocardiographic evidence of myocardial damage were included.

Over a period of one and one-half years, 122 patients were studied. These we have designated as primary patients. Each was examined for the presence of arcus senilis, xanthelasma, and xanthoma; and one or more serum cholesterol determinations were made by the method of Bloor.¹¹ There were 108 men and 14 women. Most were between 35 and 50 years of age, the youngest being 27 years and the oldest, 64 years. The average age was 45 years, the average age at onset of symptoms, 42 years. Those patients older than 50 years at the time of this investigation had developed angina pectoris prior to the age of 50 years.

We were able to study and evaluate the families of fifty of the 122 patients. By family is meant all or most of the siblings. In each of three families of six to seven siblings, we were able to study only three members. Salient features of the siblings' medical history, such as heart disease, hypertension, and diabetes mellitus, were recorded. The presence or absence of arcus senilis, xanthelasma, and xanthoma were noted and serum cholesterol determined. In a few instances, the parents and children of primary patients were studied also. It is germane to note at this point that in conducting this type of family study much difficulty will be encountered in obtaining complete or nearly complete families. Many of the patients do not know the whereabouts or health status of their siblings, especially of those living outside the United States. In the present study, additional limitations were created since many siblings were serving in the Armed Forces and were unavailable for investigation.

The range of normal serum cholesterol, according to Bloor's¹¹ method, is between 180 and 220 mg. per 100 cubic centimeters. By other methods,¹² 250 mg. per 100 c.c. is considered the upper limit of normal. For purposes of our study, however, a serum cholesterol level of at least 300 mg. per 100 c.c. was chosen as indicative of hypercholesterolemia, thus eliminating the influence of minor elevations of serum cholesterol.

RESULTS

A total of 307 serum cholesterol determinations were made. The values among the primary patients ranged from 199 mg. per 100 c.c. to 845 mg. per 100 c.c., the mean being 316 mg. per 100 c.c. (± 7.49 S.D._m). The mean serum cholesterol in this series is somewhat lower than that reported by Steiner and Domanski⁸ who found an average of 355 mg. per 100 c.c. in their small group of patients with proved coronary artery disease studied over a long period, but higher than that reported by Herrmann.⁹

Among the 122 patients, there were seventy-one (58%) whose serum cholesterol was elevated above 300 mg. per 100 c.c. (Fig. 1). The average serum cholesterol among these seventy-one patients was 365 mg. per 100 cubic centimeters. The average serum cholesterol among the remaining fifty-one patients was

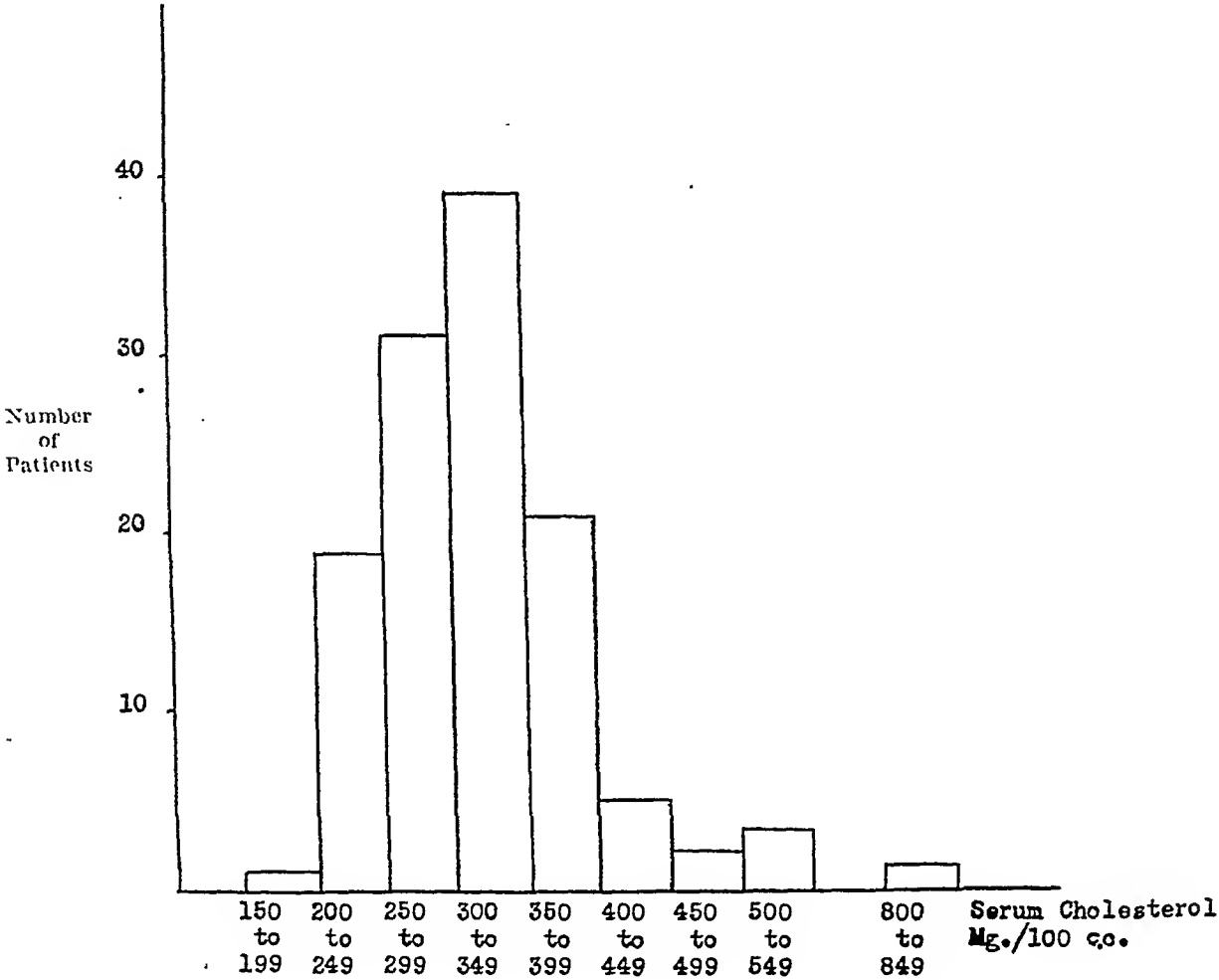


Fig. 1.—Distribution of serum cholesterol values among one hundred twenty-two patients with proved coronary atherosclerosis.

250 mg. per 100 cubic centimeters. There were twenty-two patients with arcus senilis, twelve with xanthelasma, and three with xanthomatosis. Comparing similar age groups, the incidence of arcus senilis in the presence of coronary artery disease was approximately the same in this series as in a previously reported study.³ Among the twenty-two patients with arcus senilis and coronary atherosclerosis, seventeen had elevated serum cholesterol; among the twelve patients with xanthelasma and atherosclerosis, nine had elevated serum cholesterol; while among the three with xanthomatosis and coronary atherosclerosis, all had hypercholesterolemia.

Hypertension was present in twenty-one of the 122 patients, diabetes mellitus in three, and rheumatic heart disease in two. Hypertension was found in eight of the fourteen women of the group.

Of the fifty families studied, there were fifteen (30%) in which all or most of the siblings showed an elevation of serum cholesterol. (These are the first fifteen families listed in Table I.) There were nine families in which one-half of the members available for study exhibited hypercholesterolemia, while the other half had normal cholesterol values as judged by our previously mentioned standard. In twenty-six families, there was no general tendency toward elevated serum cholesterol, even though an occasional sibling exhibited hypercholesterolemia. In a few instances the primary patient was found to have normal serum cholesterol, but the siblings had hypercholesterolemia or stigmata of disturbed lipid metabolism.

Among the fifty families, several are of special interest:

CASE 10.—H. B. P., a man 52 years of age developed angina pectoris at the age of 47 years. He exhibited arcus senilis; his serum cholesterol was 322 mg. per 100 cubic centimeters. His mother had died at 58 years of age of "heart trouble" and diabetes mellitus; three sisters had died, one at 66 years of "heart disease" and two of "strokes" at 38 and 52 years, respectively. There were two living sisters whose serum cholesterol values were elevated to 350 and 325 mg. per 100 cubic centimeters. The patient's son had a normal cholesterol.

CASE 4.—C. W., a 37-year-old man, had a cardiac infarction at the age of 37 years. His serum cholesterol was 285 mg. per 100 cubic centimeters. However, a brother who suffered a cardiac infarction at 38 years of age had a serum cholesterol of 339 mg. per 100 cubic centimeters. Two other siblings had serum cholesterol values of 322 mg. per 100 cubic centimeters.

CASE 1.—F. Z., a woman known to have hypertension, 48 years of age, had a cardiac infarction. Her serum cholesterol was 345 mg. per 100 cubic centimeters. Her mother and one sister had died of "heart attacks." Hypercholesterolemia was present in three of four living siblings, being 330, 320, and 304 mg. per 100 cubic centimeters. The fourth sibling had a serum cholesterol of 240 mg. per 100 cubic centimeters.

CASE 3.—I. F., a 48-year-old man, had a cardiac infarction. His serum cholesterol was 500 mg. per 100 cubic centimeters. There were two siblings, both of whom had hypercholesterolemia, the values being 435 mg. per 100 c.c. in a sister aged 46 years and 308 mg. per 100 c.c. in a brother aged 56 years.

CASE 8.—M. K., a man aged 43 years, had a cardiac infarction at the age of 41 years. His serum cholesterol was 327 mg. per 100 cubic centimeters. A brother had a cardiac infarction at the age of 32 years. His serum cholesterol was 318 mg. per 100 cubic centimeters. There were two sisters, aged 43 and 37 years, whose serum cholesterols were 320 and 263 mg. per 100 c.c., respectively.

CASE 11.—A 51-year-old woman had developed angina pectoris at the age of 49 years. There was xanthelasma of both upper lids. Her serum cholesterol was 362 mg. per 100 cubic centimeters. An only sibling, a sister aged 58, had xanthelasma since the age of 36 years. Her serum cholesterol was also 362 mg. per 100 cubic centimeters. A daughter, 28 years of age whom we were unable to examine was stated to be developing xanthelasma also.

CASE 37.—B. R., a woman 34 years of age, had had hypertension and coronary sclerosis for three years. Her serum cholesterol was 336 mg. per 100 cubic centimeters. Her father had died of cardiac infarction and her mother had angina pectoris. There were four siblings, one of whom,

TABLE I. SERUM CHOLESTEROL LEVELS AMONG SIBLINGS OF PATIENTS WITH CORONARY ATHEROSCLEROSIS*

NO.	PATIENT	SERUM CHOLESTEROL MG./100 C.C.	SERUM CHOLESTEROL OF SIBLINGS MG./100 C.C.						REMARKS
			SIBLING 1	SIBLING 2	SIBLING 3	SIBLING 4	SIBLING 5	SIBLING 6	
1	F. Z.	345	330	320	304	240			Sibling 5, woman, died age 46 of "heart attack." Mother died age 76 "heart attack"
9	L. K.	318	318	310	287	?			Sibling 3, woman 50 years of age, hypertension
4	C. W.	285	339	322	319	?			Sibling 2, man, hypertension
8	M. K.	327	318	320	263		?		Sibling 1, man, cardiac infarction, age 32
2	S. K.	335	350	212					Sibling 1, man 51 years of age, hypertension. Mother died age 72, hemiplegia
3	I. F.	500	435	308					
14	S. D. R.	374	303	235	?				
5	C. J.	315	325	330	?				Sibling 2, man, hypertension and auricular fibrillation
7	L. P.	300	328	241	?	?			
13	M. T. S.	336	424	308	?	?			Sibling 3, woman, died age 38, "stroke"; sibling 4, woman, died age 52, "stroke"; sibling 5, woman, age 66, died "heart disease"; mother died age 58, diabetes and "heart trouble"
10	H. B. F.	322	350	325	?	?			
11	I. S.	362	362						
15	J. N.	358	408						
6	H. R.	390	370	?					Mother died age 52, diabetes mellitus; father died, 62, "heart attack"
12	B. S.†	518	?						Four children; cholesterol values of 368, 326, 311, and 246
24	A. R.	330	296	?					Sibling 2, man, died cardiac infarction, age 41. Mother and father died of "heart disease"
27	A. C. K.	282	325						Father, age 70, has coronary artery disease
44	J. B. B.	230	300						
45	P. M.	277	366						Sibling, woman 59 years of age, has hypertension and coronary artery disease
46	C. R.	340	330	280	274				
47	M. S. L.	342	240						
48	A. S.	314	232						Father died age 58, cardiac infarction
49	J. W.	265	343						
50	J. B.	330	268						Father died age 57, cardiac infarction

40	E. R.	357	350	292	283	260	246	?	Sibling 1, man 50-years of age, has coronary sclerosis
25	P. K.	263	270	248	261	?	?	?	
18	I. T. K.	220	325	284	257	232	220	?	Sibling 1, man aged 38, has arcus senilis
21	J. W. W.	425	306	274	257	168	140	?	Father, aged 60, died coronary artery disease
28	H. A.	272, 238	357	262	241	220	220	?	Sibling 1, woman, aged 48, hypertension and angina
31	I. R.	311	196	178	168	?	?	?	pectoris; sibling 2, man aged 46, hypertension;
34	I. G.	199	256	246	224	?	?	?	sibling 3, man aged 54, angina pectoris
23	A. B.	351	300	286	?	?	?	?	Sibling 1, man aged 40 years, has marked arcus senilis;
37	B. R.	336	357	241	227	207	?	?	father died 58, cardiac infarction; mother has angina pectoris
16	H. N.	284, 256	278	263	187	?	?	?	All siblings have hypertension
20	J. P.	350	277	210	206	?	?	?	
41	S. D.	333, 355	245	214	198	?	?	?	
29	S. K. B.	236	270	217	?	?	?	?	
17	M. R. S.	332	293	260	255	?	?	?	
22	A. H.	289	320	276	246	?	?	?	
30	O. S.	232	278	263	184	?	?	?	Mother, age 53, hypertension and angina pectoris
43	J. H.	224	238	212	165	?	?	?	Father died age 46, arteriosclerosis. Sibling 1, woman,
26	H. K. M.	260	270	244	?	?	?	?	hypertension and arteriosclerosis
32	J. L.	215	182	167	?	?	?	?	Sibling 2, man, died cardiac infarction at 58. Both
33	G. S. S.	360	292	261	?	?	?	?	parents died of hypertensive arteriosclerotic heart disease
36	I. K.	225	216	208	?	?	?	?	Mother has coronary artery disease, father has hyper-
39	B. G.	330, 330	241	202	?	?	?	?	tension
19	N. M.	220	200	?	?	?	?	?	Sibling, man, cardiac infarction, age 40
35	H. S. B.	287	297	?	?	?	?	?	Sibling, man, had cardiac infarction, age 49
38	S. P. P.	254	207	?	?	?	?	?	Father, age 67, has coronary sclerosis and cholesterol
42	M. C.	269	264	?	?	?	?	?	of 232

*The first fifteen families listed are those in which hypercholesterolemia was present in all or most siblings. The next nine families listed are those in which one-half the members exhibited hypercholesterolemia and one-half had normal serum cholesterol. The remaining twenty-six families are those in which there was no general tendency to hypercholesterolemia, although an occasional sibling exhibited hypercholesterolemia.

+ ? indicates sibling unavailable for study.

†Since there were no living siblings, the children were studied

a 40-year-old man, had arcus senilis and a serum cholesterol of 357 mg. per 100 cubic centimeters. The other siblings had normal serum cholesterol values.

CASE 12.—B. S., a 56-year-old woman, who had diabetes mellitus, hypertension, and angina pectoris for many years, suffered a cardiac infarction. She exhibited xanthelasma. Her serum cholesterol was 518 mg. per 100 cubic centimeters. Her husband was stated to have xanthelasma also. Three of their four children had hypercholesterolemia, the values being 311, 326, and 368 mg. per 100 cubic centimeters. Two of them exhibited xanthelasma. The serum cholesterol of the fourth child was 246 mg. per 100 cubic centimeters.

CASE 24.—A. R., a man 36 years of age, had a cardiac infarction at the age of 34 years and again at the age of 36 years. His serum cholesterol was 330 mg. per 100 cubic centimeters. His mother and father had both died of "heart attacks"; his brother had died of cardiac infarction at the age of 41 years. The serum cholesterol of a living sister, 45 years of age, was 296 mg. per 100 cubic centimeters.

CASE 28.—H. A., a man 40 years of age, had a cardiac infarction. He exhibited marked arcus senilis and a serum cholesterol of 272 mg. per 100 cubic centimeters. His father had heart disease. There were five siblings, one of whom, aged 38 years, had arcus senilis and a serum cholesterol of 357 mg. per 100 cubic centimeters. Serum cholesterol values were normal among the remaining siblings.

CASE 41.—S. D., a 47-year-old man, had a cardiac infarction. He exhibited marked arcus senilis. His serum cholesterol values were 333 and 350 mg. per 100 cubic centimeters. Although the serum cholesterol value was normal in all four siblings, one of them, aged 42 years, exhibited marked arcus senilis.

The following case illustrates the gradual evolution of several manifestations of hypercholesterolemia in a young man:

CASE 48.—A. S., a 31-year-old man, was first seen in 1937 at the age of 24 years, three months after his father, aged 58, had died under observation of a coronary artery occlusion. In 1932, he had had "nervous indigestion," and in 1934, symptoms of peptic ulcer although gastrointestinal x-ray studies were normal. About three months prior to his first examination, while taking nitrous oxide for a tooth extraction, he experienced severe precordial pain with every heart beat, but had no residual pain or symptoms after the extraction. Two months later, a tooth was extracted under novocain anesthesia and he fainted three hours after the extraction. Subsequently he felt very tense and nervous for a number of days. When first seen, physical examination was completely negative; the blood pressure was 130/90. The electrocardiogram showed a flat T wave in Lead I and negative T waves in Leads II and III. He had no significant cardiac symptoms subsequently, but developed a severe psychoneurosis for which he received psychiatric treatment. A year later, his only cardiac symptoms were palpitation and occasional stabbing precordial pain. At this time the T wave in Lead II was flat, and the T wave in Lead III still negative. He had no significant symptoms until four years later, when he had a number of attacks of precordial pain radiating down the left arm. There was no change in the physical or electrocardiographic findings. For the first time, small xanthelasmas were observed at the inner canthi of both eyes. He was not seen again until the age of 31 years, when he complained of sharp left parasternal pain and a sense of suffocation on walking rapidly and with excitement. There was no change in the physical examination or in the electrocardiogram. There were large xanthelasmas of both upper eyelids and a beginning arcus senilis. The serum cholesterol at this time was 350 mg. per 100 c.c. and the cholesterol esters, 250. His brother, aged 29 years, was apparently well and had a serum cholesterol of 232 mg. per 100 cubic centimeters.

DISCUSSION

The role of cholesterol in the production of atherosclerosis has been a matter of contention since 1911, when Anitschkow¹³ produced lesions resembling human

atherosclerosis in rabbits by feeding them cholesterol dissolved in oil. Subsequently, Leary^{14,15} and many others confirmed these experiments, some of which were extended to include certain omnivorous,^{16,17} as well as herbivorous, animals. Similar lesions have been produced lately in dogs by modifying the activity of the thyroid gland during cholesterol feeding.¹⁸ Accompanying the atherosclerosis incident to feeding experimental animals large amounts of cholesterol, there appears a marked hypercholesterolemia. Because cholesterol feeding in man does not result in hypercholesterolemia, the significance of animal experiment has been questioned. However, feeding small amounts of cholesterol to rabbits over long periods will produce atheroma even though there is no elevation of serum cholesterol.¹⁵ Since absolute elevation of serum cholesterol is not a prerequisite for experimental induction of atherosclerosis, other factors have been implicated, such as the rate of transport of cholesterol after its alimentary absorption or inefficiency of cholesterol metabolism itself. An extreme point of view is taken by Thannhauser¹⁹ who believes that even primary essential xanthomatosis is not caused by a disorder of intermediary cholesterol metabolism, but that the metabolic disturbance of cholesterol lies within the reticular cells themselves. He states that hypercholesterolemia in itself does not cause the syndrome because xanthomas may develop while blood cholesterol is normal and cites as support the existence of a normocholesterolemic form of xanthomatosis. He believes that the development of atherosclerosis in patients with diabetic hyperlipemia is similar in pathogenesis to that produced in hypercholesterolemic rabbits, and contrasts it with the intrinsic formation of foam cells in xanthomatous tissue in primary essential xanthomatosis. He denies that pathologic hyperlipemia can be concerned in the development of atherosclerosis or atheromatosis in general. Against these conclusions may be posed the known fact that, in many different forms of lipidoses and xanthomatoses, atherosclerosis is encountered almost exclusively in those associated with hypercholesterolemia, that is, in xanthelasma, xanthoma tuberosum and planum, tendon xanthoma, and in xanthomatous biliary cirrhosis. These are all associated with hypercholesterolemia at some stage of their development. Atheromatosis occurs early and extensively in diabetics with hyperlipemia and hypercholesterolemia; it occurs frequently in children with hypercholesterolemia due to nephrosis; it occurs in patients with myxedema in whom blood cholesterol is elevated. Pathologic studies by Ashoff²⁰ and Leary²¹ revealed foam cells indistinguishable from xanthoma cells in early atherosclerotic lesions. For a comprehensive discussion of the problem of the pathogenesis of atherosclerosis and extensive bibliographies, the reviews by Hueper²² and Katz and Dauber²³ should be consulted.

Regardless of the *modus operandi*, the clinical association of elevated serum cholesterol and atherosclerosis of the coronary arteries revealed by previous studies^{4,7,9} and the present one would appear to be more than accidental. The occurrence of arcus senilis in young people with coronary artery disease should probably be regarded in the same light too, and not as a sign of premature senescence.

The occurrence of elevated serum cholesterol in one-third of the families of patients with coronary atherosclerosis suggests that among the hereditary factors that predispose to arteriosclerotic heart disease, a disturbance of lipid metabolism may play as significant a part as either hypertension or an inherited peculiarity of the coronary artery intima.²⁴ A priori, one would not expect an hereditary abnormality to occur in all or most members of every family. The variations in the familial incidence of coronary atherosclerosis may be accounted for by the degree of dilution or concentration of the tendency to abnormal cholesterol metabolism. If only one marriage partner has hypercholesterolemia, the tendency to this disorder will be diluted and fewer children will be affected; if both have hypercholesterolemia, the tendency will be intensified.¹ Thus the scattered instances of hypercholesterolemia in our material may have more significance than appears on the surface. Quite similar trends are observed in the hereditary distribution of diabetes mellitus.

The burden of a disturbed cholesterol metabolism may possibly be eased by dietary adjustment (low fat—low cholesterol diet), lecithin feeding, or other techniques such as the administration of thyroid substance and other compounds. By feeding lecithin to patients with hereditary xanthomatosis, depression of serum cholesterol may be obtained, especially when a cholesterol-poor diet is taken concomitantly.²⁵ This approach is promising and deserves further study.

The role of the thyroid hormone in the pathogenesis of atherosclerosis has been carefully investigated and it is known that thyroid administered simultaneously with cholesterol will prevent experimental atheromatosis in rabbits.²⁶ Conversely, thyroidectomy enhances the ease with which hypercholesterolemia and atheroma may be induced by cholesterol feeding.²⁷ Recently thiouracil has been administered to modify the function of the thyroid gland of dogs fed cholesterol in oil. Lesions resembling human atherosclerosis and arteriosclerosis in distribution and morphologic characteristics followed the hypercholesterolemia thus produced.¹⁸ Davis and associates⁷ investigated the basal metabolic rates of their patients with angina pectoris and hypercholesterolemia, but did not find any significant depression of thyroid function. Among their patients with coronary atherosclerosis, the average basal metabolic rate was minus 8 per cent, while among a comparable group of normal individuals, the basal metabolic rate was minus 13 per cent. Lerman and White,¹⁰ on the other hand, in a recent study found low basal metabolic rates in about one-half of their patients with coronary artery disease and hypercholesterolemia and believed that the administration of thyroid substance benefited them. Further investigations in this direction are warranted.

Mention should be made of potassium iodide and organic iodide which, like thyroid substance, prevent the development of experimental atheroma.²⁸ However, they do not prevent hypercholesterolemia from developing. Perhaps a resurrection of the study of iodine compounds in relation to the prevention of atherosclerosis is timely.

In any event, since hypercholesterolemia reflects a metabolic disturbance, effort might well be expended in modifying its influence on the vascular system much as one attempts to obviate the complications of diabetes mellitus by diet and insulin. A pharmacologic counterpart to insulin for the treatment of hypercholesterolemia is not beyond the realm of possibility. By vigorously pursuing the various avenues of approach opened by the previously mentioned experiments, it may be possible to modify eventually one of the substrates of atherosclerosis and thereby reduce the incidence of coronary artery disease and death from cardiac infarction.

SUMMARY

Serum cholesterol was found to be elevated over 300 mg. per 100 c.c. in seventy-one members (58 per cent) of a group of 122 patients with proved coronary atherosclerosis whose disease began under the age of 50 years. The average serum cholesterol for the entire group of 122 patients was 316 mg. per 100 c.c. (± 7.49 S.D._m). The average serum cholesterol for the seventy-one patients who exhibited hypercholesterolemia was 365 mg. per 100 c.c., and the average among the remaining fifty-one patients was 250 mg. per 100 cubic centimeters. Arcus senilis was exhibited by twenty-two, xanthelasma by twelve, and xanthomatosis by three of the group. The great majority with these stigmata had elevated serum cholesterol levels.

Hypercholesterolemia (serum cholesterol of 300 mg. per 100 c.c. or more) was found in all or most of the siblings of one-third of fifty families of patients with coronary atherosclerosis. In nine more families, one-half of the siblings exhibited hypercholesterolemia.

This study lends support to previous clinical investigations and indicates that a disturbance in cholesterol metabolism is probably concerned in the genesis of some instances of coronary atherosclerosis. It also suggests that altered cholesterol metabolism may be the common denominator in most patients who have coronary artery disease and arcus senilis, or coronary artery disease and xanthelasma.

One of the hereditary factors responsible for arteriosclerotic heart disease may reside in abnormal cholesterol metabolism. Since therapeutic measures for correcting this metabolic disturbance may reasonably be anticipated, further investigations paralleling the present one are desirable.

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PRIMARY VASCULAR TUMORS OF THE PERICARDIUM

A REPORT OF TWO CASES

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PPRIMARY pericardial tumors are distinctly rare. Yater¹ and Monckeberg² noted that they are usually sarcoma or lipoma. Much of the literature of the pericardial tumors deals with the group of problematical serosal endotheliomas or mesotheliomas. We wish to limit our discussion to a study of the vascular tumors of the pericardium. We are omitting all other tumors, including the controversial mesothelial group. To simplify this presentation further, we wish to exclude such vascular tumors as occur in portions of the heart other than the pericardium. Chronic inflammation with pseudoglandular spaces or prominent vascular channels in granulation tissue or in organization of blood clot, such as occurs so often in auricular thrombi, do not apply to the two instances reported here.

PRESENTATION OF CASES

CASE 1.—The first case is one of benign cavernous angioma noted as an incidental finding in a patient who died of peritonitis following an operation for adenocarcinoma of the cecum.

This tumor was 1.0 cm. in diameter and presented itself as a localized deep-red discoloration in the epicardium of the left ventricle in the sulcus between the latter and the left auricle. The mass on section measured 1.0 by 0.25 centimeters. It was soft and showed some fine septa. It is significant that this patient also showed an identical cavernous angioma in the liver and an incidental leiomyoma of the kidney capsule extending into the kidney.

Microscopically, the tumor, sharply demarcated from surrounding fat tissue, consisted of large, thin-walled cavernous spaces filled with blood clot. Some of the channels showed thrombi. No reaction was noted in the pericardium.

Discussion: Tumors of this type in the pericardium have been described by Lefas,³ Timme,⁴ and Bencini.⁵ Bencini described two cases, but he classified one as a pseudoangioma. He also mentioned a case described by Pommer as a complex vascular tumor which was called an angiofibroleiomyoma. This is of interest because it implies an origin from an embryonal rest. Bencini also quoted a case of Von Hoch, called a venous angioma, which he found mentioned by

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Monckeberg.² The case of Redtenbacher⁶ may represent a malignant metastasizing cavernous angioma of the pericardium. The gross description of the primary lesion of the pericardium and the metastasis to the lungs definitely suggests a cavernous structure. The absence of a microscopic description makes it difficult to rule out a proliferating endothelial component of the neoplasm.

Tumors of this cavernous type are found elsewhere in the heart. Schuster⁷ presented a tumor 2.5 by 1.5 cm. in a papillary muscle. Train⁸ described a cavernous angioma, which reached the size of a hazel nut, in the interventricular septum. Muir⁹ referred to a tumor "of considerable size in the upper margin of the right ventricle." Rau¹⁰ reported a collection of ten cavernous channels in the region of the fossa ovalis. The authors have encountered several varixlike lesions of this type in this location.

The cases of Timme and Bencini, like our own, were incidental findings. In the patient of Lefas, death occurred suddenly because of the rupture of one of the vascular channels with bleeding into the pericardial cavity and cardiac tamponade. Bleeding may occur slowly, with a more prolonged period of symptoms. The case of Redtenbacher was of this nature with a prolonged period of progressive decompensation and venous engorgement.

CASE 2.—The second case is that of a progressive invasive cellular angioendothelioma with hemorrhage. A very similar instance was reported by Scheidegger¹¹ and the case of Redtenbacher may well represent another example. The gross features of both these instances are remarkably identical with the case we are presenting. Because of the significant clinical features, the history of this case is given in detail.

D. De J., a 27-year-old athletic white man, noted vague weakness during strenuous tennis matches. On several recent occasions, he "could not catch his breath." Such an episode occurred on May 6, 1942, and that night he noted pain in the stomach. He then became nauseated and vomited. His family physician found an enlarged heart and consulted with Dr. Daniel Porte,* a cardiologist. Physical examination at this time revealed no heart murmurs; a split sound at the apex; the aortic second sound louder than the pulmonic second sound; blood pressure, 108/76; and weight, 170½ pounds. The electrocardiogram was not unusual (Fig. 1,A). The heart was enlarged to the right and left on fluoroscopy. On July 14, 1942, he was admitted to the hospital complaining of constricting and choking sensations in the throat. He ran a septic temperature varying from 99° to 103° Fahrenheit. Electrocardiographic examination on July 18, 1942, showed inverted T waves in Leads I and II and a small R wave in Lead CF IV (Fig. 1,B). On July 24, 1942, engorged neck vessels, puffy face, prominent chest veins, distant heart sounds, and a blood pressure of 114/88 were noted. Roentgenographic examination showed moderate increase in the size of the cardiac area, the cardiac measurements being: medium right diameter, 6.5 cm.; medium left diameter, 3.0 cm.; and the width at the base of the chest, 34.0 centimeters. Diffuse clouding was seen in the cephalic half of the left lung field, with the most marked density located centrally. The remainder of the lung field was clear but the lung markings were exaggerated. On July 26, 1942, a cough productive of bright red sputum developed. Pulmonary infarction and pericardial effusion were suspected. On Aug. 3, 1942, a second roentgenograph showed no change in size or contour of the enlarged heart, approximately 75 per cent resolution of the area in the left upper lobe, and a trace of pleural fluid at the left base (Fig. 2). Both thoracentesis and pericardiocentesis were dry. Blood cultures were negative. The sedimentation rate was 9.0 mm.

*We are indebted to Dr. Porte for the clinical details of this case.

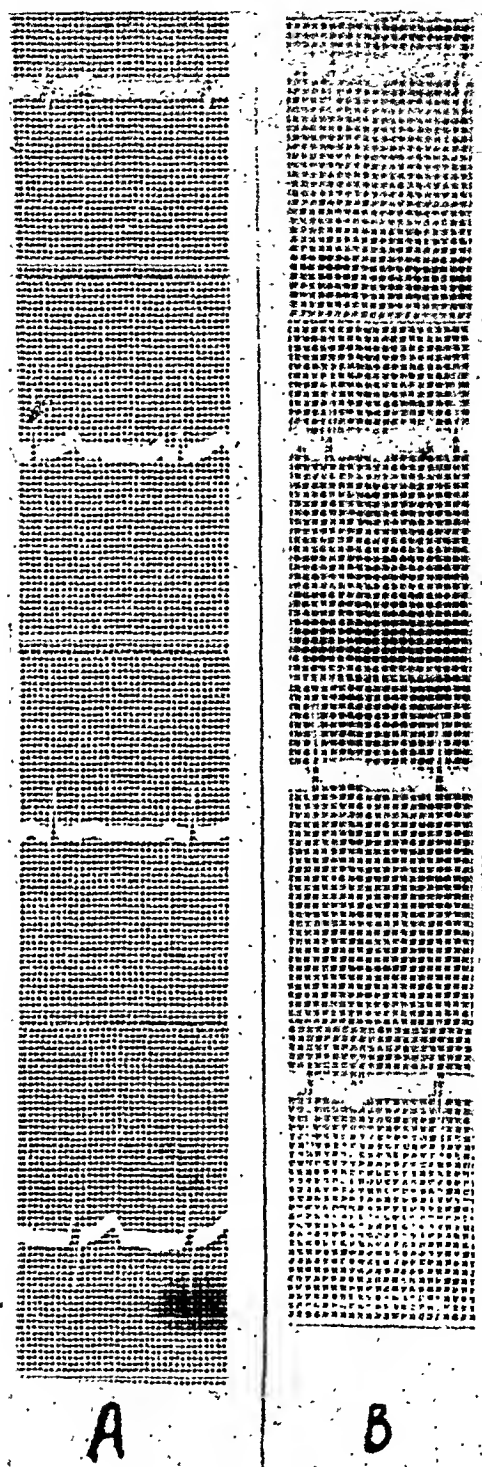


Fig. 1.—Electrocardiogram taken 130 days before death, marked A at left is not unusual; one made seventy-three days later, at right marked B, shows inverted T waves, Leads I and II, and small R wave in CF₄.

at the end of one hour. The blood count showed 3.57 million erythrocytes and 7,900 leucocytes per c.mm.; of the latter, 55 per cent were polymorphonuclear leucocytes and 45 per cent, lymphocytes. The hemoglobin content of the blood was 71 per cent.

He left the hospital Aug. 24, 1942. A downhill course followed and he expired Sept. 3, 1942.

Pathologic Findings: Autopsy revealed the pertinent pathologic findings to be limited to the heart. In addition, the deceased showed a moderate ascites, bilateral hydrothorax, marked



Fig. 2.—Roentgenogram made thirty-one days before death.

passive congestion of liver suggesting cardiac cirrhosis, multiple pulmonary infarcts, and a left axillary vein thrombus. No metastasis to other organs was found.

The heart, massively enlarged and adherent to the surrounding structures, measured 21 by 15 by 11 cm. (Fig. 3). The pericardial cavity was completely obliterated by thin, yet firm, adhesions. The parietal pericardium was stripped with difficulty from the visceral layer, but a distinct line of cleavage was maintained. It is significant that no free blood or organized clot was found within the obliterated potential cavity.

The variation in hue and consistency of the mass that thickened the epicardium and distorted the contour of the heart and its chambers was so marked as to make any attempt at localized description serve no useful purpose. Much of the distorting mass was frankly blood clot. In general, the large locules and cystic areas were found filled with such blood clot. Other areas showed rounded fibrin masses bearing a relationship to encircling paler trabeculae of fibrous or fibrin septae. In some zones, a spongy, porous character was noted in the tissue. In others, granular and homogeneous inspissated fibrin material was suggested. In still other areas, a firm consistency and a friable pale granular tissue suggested compact cellular tumor islands. The latter zones were indefinitely demarcated and accounted for only a small portion of the distorted, discolored epicardial mass seen grossly.

When the parietal pericardium was stripped, the heart muscle was found encased in an encircling bloody, discolored, tumefied visceral pericardium. This hemorrhagic mass involved most

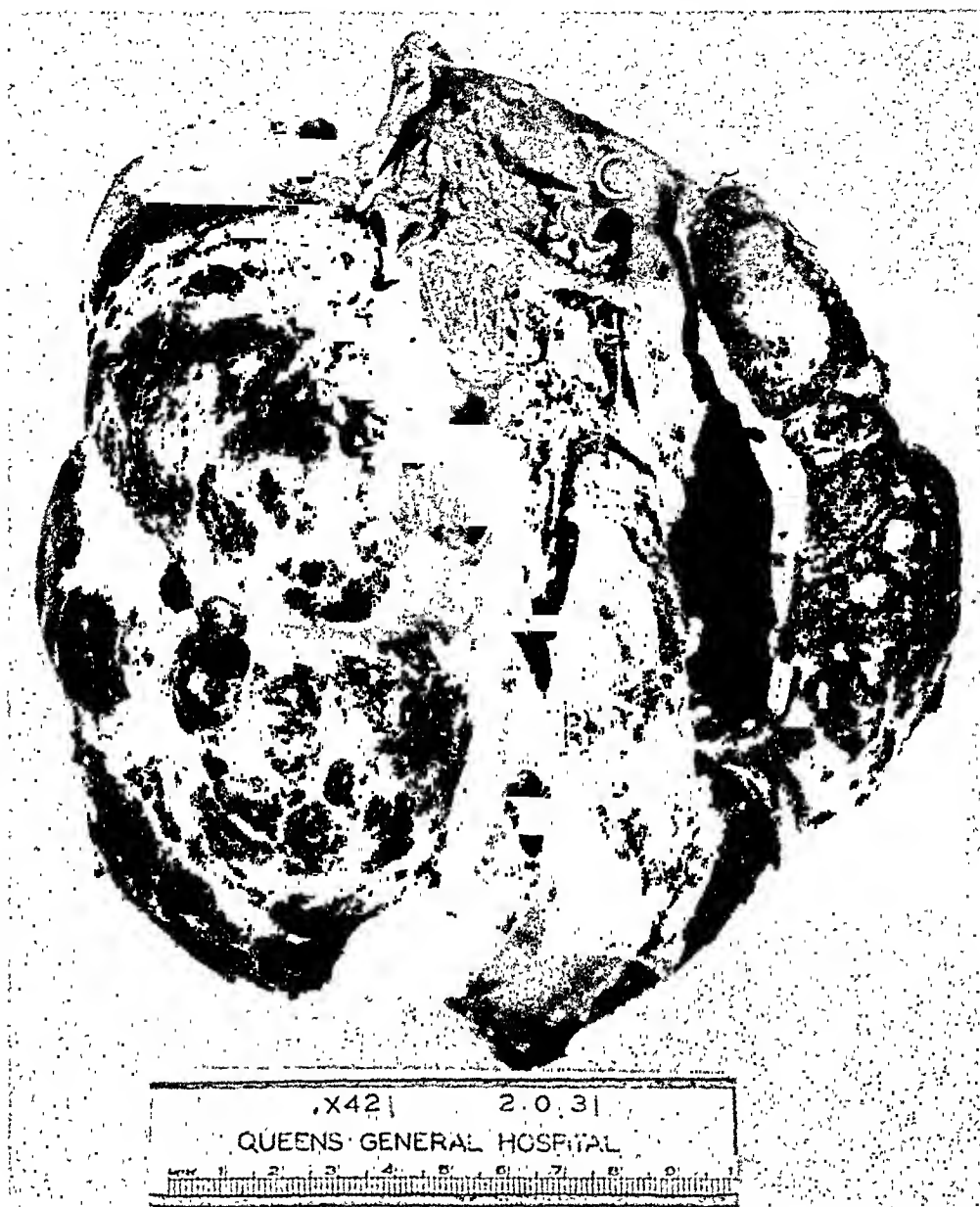


Fig. 3.—Posterior aspect of heart. A to B, auriculoventricular groove with transsection just to one side of the interventricular septum. Compression of superior vena cava by tumor at C with right auricle and inferior vena cava exposed below.

of the visceral serosal coat, penetrating here and there to the adherent parietal layer, particularly toward the apex. The heart itself was distorted, rounded, and globular in shape. The outlines of the heart chambers were sharply demarcated externally by depressed grooves (Fig. 3). The entire outer surface was red. A preserved visceral pericardial serosa could be made out except where the denuded surface had been torn in the separation of the parietal layer.

In general, the most marked distortion was found at the base. Here the hemorrhagic, tumor-like material encircled and distorted the entire posterior wall of the right auricle markedly, and of the left, to a lesser degree. It compressed and narrowed the mouths of the vena cava (Fig. 3,C) and the pulmonary veins, encircling the aorta and the pulmonary artery in the form of a thick layer on the posterior aspect (Fig. 4). These hemorrhagic zones merged with a similar area of involvement on the posterior aspect of the right and left ventricles. Anteriorly, the auriculoventricular groove on the right side was preserved and even exaggerated. Above the groove, the tumor thickening measured fully 5.0 cm. in the region of the auricles. Below the groove, the distorted epicardium overlying the left ventricle measured 3.5 to 4 cm. (Fig.



Fig. 4.—Posteroanterior section through the left ventricle and aorta, bisecting the right coronary ostium and cutting across the pulmonary artery. At *A*, the arrow points to the left half of the right coronary ostium. The probe is inserted into the right coronary artery. *B* shows the left ventricle and *C*, the auriculoventricular groove. The epicardium of the left auricle above is markedly involved.

4,*B*). The epicardium along the auriculoventricular groove proper measured only 0.5 cm. in thickness (Fig. 4,*C*).

The hemorrhagic material at the base of the heart extended to involve the base of the aorta where it was 3.0 to 5.0 cm. in thickness and was sharply delimited by the line of reflection of the parietal pericardium. The basilar involvement also completely encircled the pulmonary artery, beginning just above the level of the pulmonary valves. Here it measured 3.0 to 5.0 cm. in thickness. At this point, the tumor mass seemed to extend beyond the pericardial reflection to the parietal layer proper for a short distance.

In the region of the ventricles, the tumor was definitely thinner as compared to the auricular or basilar involvement (Fig. 4,*B*). The right ventricle was involved posteriorly and laterally where the tumor was quite thick again, measuring 4.0 to 5.0 cm. in some areas. The chamber of the right ventricle had its contour distorted by the inward bulging of the tumor. Anteriorly, the epicardium of the pulmonary conus adjacent to the right ventricle and the most proximal pulmonary artery was least involved. The epicardium here measured only 5.0 mm. in thickness (Fig. 4,*C*) and showed serous edema of the fat. The left ventricle showed marked distortion by the encircling reddish tumor mass (Fig. 4,*B*) except anteriorly, where again less distortion existed. This relatively uninvolved zone of left ventricular epicardium included the apex and basilar portion of the ventricle adjacent to the anteriorly placed uninvolved right ventricle and pulmonary conus already described.

The myocardium throughout showed no evidence of invasion by the tumor tissue grossly, but the heart wall seemed stiffened and less pliable. The muscle of the left ventricle measured

15 to 16 mm. in thickness. The chambers seemed small in proportion, especially those of the ventricles. The tumor at the base of the heart encircled and compressed the mouth of the right coronary artery (Fig. 4, A). The rest of the coronary arteries and the coronary sinus showed no alteration.

The appearance definitely indicated that the tumor was not in the pericardium but in the visceral layer, and limited to this zone except for relatively small areas of extension to the regional myocardium and the parietal pericardium. The stripped parietal pericardium was slightly thickened throughout, and presented sharply delimited areas of thickening which appeared as red protrusions. There were more than a dozen such protrusions, varying in size from 0.5 to 1.0 cm. in diameter. On section, they were found to be lobulated and porous and contained clotted blood. Other protuberant nodules were made up of firm, granular white tissue and suggested altered fibrin, compact cellular zones of vascularization, or solid zones of tumor tissue. The nodules could be separated from the parietal pericardium with difficulty through a cleavage plane corresponding to the original serosal layer of the pericardium, leaving rounded pitted depressions covered by adherent hemorrhagic material. Both visceral and parietal pericardium on their opposed surfaces showed a brownish staining produced by a fine granular film suggesting fibrin.

Microscopic Description: The microscopic sections taken throughout the mass were stained by hematoxylin and eosin, Mallory's phosphotungstic acid, and van Gieson and Mallory's connective tissue stains. In many sections only blood clot could be made out. Some of the clot showed mainly fibrin with hemolysis of the red cells and distinct lamellation. Other areas showed fresh nonlamellated clot. Much of the trabeculation referred to in the gross description represented septa of older fibrin contrasted with fresh red blood coagulum. Some of the septa were fibrous. Much of the blood clot was found within dilated cavernous channels lined by hypertrophic and hyperchromatic small-celled tumor tissue. In some areas, the fibrous septa were lined by a single layer of such cells. The living tumor tissue of the cavernous channels showed zones of heaped-up, proliferating, compact cellular tumor, which protruded as a nubbin into the enclosed blood clot. There was nowhere seen a true papillation with delimited papillary epithelial-like tissue. The papillary masses were revealed as heaped-up cellular areas of tumor tissue without any coherent histologic organization. Compact cellular zones of tumor tissue were seen in small foci and suggested the complete filling of previously existing cavernous channels, with little blood clot present.

The cytology of the tumor tissue was also variable. In the main, the tissue suggested a sarcoma. Only the nuclei were discernible in most of the tumor, with the cytoplasm indefinitely outlined, indeterminate, scant, and often suggesting a syncytium. The linear outline and shape of the nuclei varied markedly. Most of the chromatin was found in the nuclear membrane, which appeared as a uniformly sharp line. The remainder of the nuclei showed relatively small nucleoli and only small flecks of chromatin. This gave the nucleus a vesicular appearance, despite evident hyperchromatism. Some tumor cells were rounded, with limited borders and deep staining eosinophilic cytoplasm. No bizarre pleomorphism or atypical giant cells were found.

In some zones, smaller but definite tumor-lined vascular channels (Fig. 5) were filled with red blood cells or clot of a post-mortem character. Such areas merged with others where a distinct resemblance to granulation tissue was evident. Some of the capillary buds merged with solid columns of tumor cells, with the demonstrable central vacuolization suggesting an actual embryonic process of capillary channel formation. All of these zones of formative vascular channels merged with compact cellular diffuse tumor-cell areas.

In the region of the left ventricle, the tumor tissue was cellular and solid and invaded the underlying myocardium, in several sections, but only for short distances. The involved muscle showed atrophy. The living capillary endothelium between the muscle bundles showed progressive changes of transition to tumor tissue. In the regions of the left auricle, toward the apex, and on the masses found on the stripped parietal pericardium, the tumor showed a prominent cavernous structure with little tumor tissue, which was limited to the lining of such channels. The tumor overlying the right auricle showed outstanding cellularity. The cellular tissue here presented the most marked anaplasia, with irregularity in the contour and staining of the nuclei.

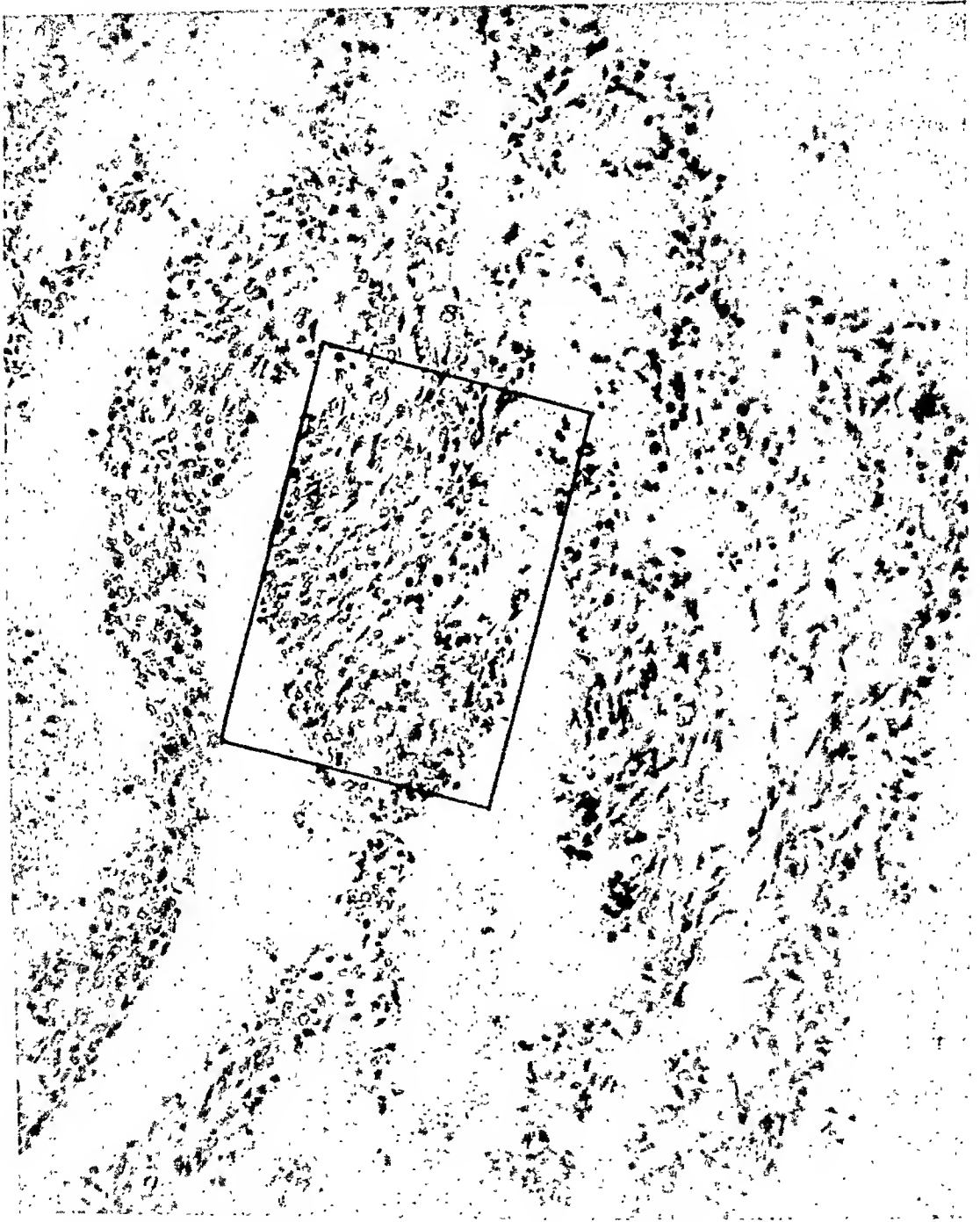


Fig. 5.—H & E microphotograph, $\times 375$, of tumor tissue in epicardium which demonstrates the tendency to form vascular spaces and solid masses of cellular tissue showing elongated vesicular nuclei with prominent nucleoli.

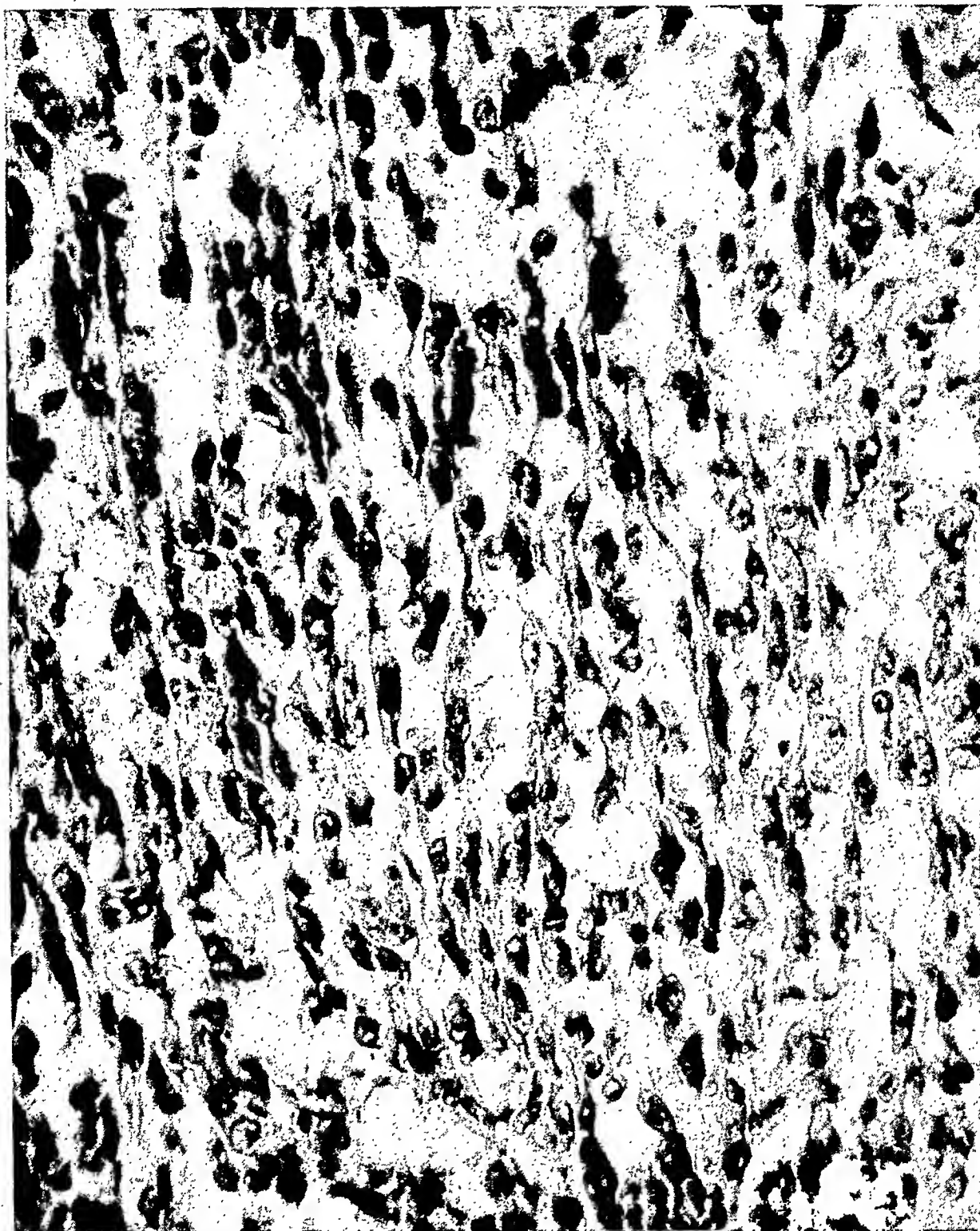


Fig. 6.—Higher power, x875, showing compact cellular areas of characteristic cells with distinct nuclear membranes and prominent small nucleoli and distinct, prominent vacuolization suggesting mechanism of channel formation.

No hematopoietic tissue was encountered in any of the capillary areas or larger lumina or in the more cellular zones.

The lungs showed an area of infarction undergoing resolution and organization. In the remaining lung tissue, there was some fibrosis with prominent heart failure cells and some vascular sclerosis. Adherent fibrin coated the pleura. The liver showed some edema and marked congestion but no true cirrhosis.

Discussion of Case 2: The case of Scheidegger¹¹ presented gross and microscopic features quite similar to this case. His tumor, however, metastasized to the mediastinal lymph nodes, the liver, the lung, and particularly to the pleura. One metastatic focus involved a pre-existing cavernoma of the liver. There is special significance to the localization of this metastasis. Such metastasis to cavernomas has been frequently found by us in many forms of malignancy. The case of Redtenbacher also showed metastasis to the lung, particularly the edges of the lower lobes. As noted, the inadequacy of the descriptive detail makes the exact classification of this tumor difficult. It is quite possible, in view of the metastasis present, that solid endothelial proliferative areas could have been seen on microscopic study. An endothelioma of the pericardium of serosal cell origin was described by Hines and Nolan.¹² Their description, however, noted vascular channels with blood content, and the possibility of a vascular endothelioma must be entertained.

DISCUSSION

Tumors of this structure have been described as occurring in other parts of the heart. Such angioendotheliomas or angiosarcomas have been noted most often as originating from the auricular wall, particularly from that of the right auricle. There exists an abundant literature dealing with the problem of differentiation of these tumors from true myxomas and vascularized organized thrombi. It is our own conviction that many reported cases of angioendotheliomas of the heart represent instances of vascularization of thrombi, rather than true neoplastic blood vessel proliferations or aggressive endothelial tumors. However, there are instances in the literature of metastatic foci which seem to confirm biologically the morphologic appearance of true malignant neoplasia for some of the reported cases.

Orsos¹³ attempted a classification of the vascular tumors and described tumors of this type with very similar histologic features as gemmangiomas. None of his eleven cases involved a pericardial neoplasm.

From the standpoint of the origin of these tumors, the finding of coexisting angiomas elsewhere deserves consideration. The first case showed a cavernoma of the liver and a leiomyoma of the kidney. In the case of Scheidegger, several vascular cavernous angiomas were found in the liver. Redtenbacher described a papilliferous pigmented nevus of the skin on the shoulder. His description does not favor a vascular type of nevus. The thought is a compelling one that these tumors represent vascular anomalies or may originate from pre-existing

nevi or vascular rests. Such islands, or rests, in the pericardium may acquire progressive active growth features and metastasize much as the ordinary malignant skin angiomas are known to do. We do not mean to imply that the malignant angioendotheliomas originate from the cavernous structures. It is our impression, rather, that they represent two independent entities. The capillary nevi, in general, are known to become aggressive more often and probably originate from a nevus rest which has a capillary structure at the outset. Cavernous angiomas are considered hamartomas and rarely present metastasis or progressive growth in the ordinary sense. An occasional cavernoma will metastasize to lung or lymph nodes, as in the cases depicted by Ewing.¹⁴ The case of Redtenbacker may well represent such a metastasizing malignant form of cavernous angioma originating in the pericardium.

Mahaim¹⁵ considers this neoplasm, at least in its counterpart described by Scheidegger, as a "very vascular coelotheliome." His classification which grouped the malignant pericardial tumors under the general heading of "malignant coelotheliome," though quite satisfactory clinically, represents an oversimplification from the pathologic standpoint.

Yater attempted a delineation of a clinical picture for tumors of the pericardium. It would seem that the clinical picture can present such marked variations that the proposed isolation of a specific clinical entity is of doubtful assistance. The clinical course will depend upon the proportion of hemorrhage in the tumor mass and its rapidity of occurrence, as well as the presence or absence of an obliterated pericardial cavity. In some of the cavernous tumors a rapid tamponade causes sudden death, as in the case of Lefas. In the cases of Scheidegger and Redtenbacker, an increasing decompensation with vena caval compression was slowly progressive, with sufficient time for metastasis to occur. In the second case presented here the course was rapidly progressive and death occurred before metastasis had taken place. If a previously healthy individual shows, without known cause, a rapid evolution of the symptoms of decompensation and an enlarged cardiac shadow, a pericardial tumor should be considered.

CONCLUSION

1. A cavernous angioma of the pericardium and a case of a progressive malignant angioendothelioma of the pericardium have been presented.
2. The literature dealing with pericardial vascular tumors has been reviewed and only three definite cases of the cavernous form and two specific instances of malignant angioendotheliomas were found.
3. The possible origin of such tumors has been discussed.
4. The variation in the clinical course has been analyzed.

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SUDDEN AND UNEXPECTED NATURAL DEATH

II. CORONARY ARTERY SCLEROSIS

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THIS is the second in a series of papers on sudden and unexpected natural death, verified at necropsy, in 2,030 consecutive cases in the Office of the Chief Medical Examiner, New York City, for the Borough of Manhattan. In the first paper,¹ a survey was made of the circumstances under which the Medical Examiner assumes jurisdiction, of the various pathologic conditions encountered, and of the sex, age, and racial distribution of the cases under consideration. That survey may be briefly summarized.

The 2,030 cases were observed during the period from Jan. 1, 1937, to June 30, 1943; death was unexpected in that the victims were apparently healthy at the time of death, and sudden because death took place usually within twenty-four hours after the onset of symptoms. The designation "natural death" indicates that death resulted exclusively from disease unassociated with external violence or poisoning.

The material was gathered from a community the population of which is made up of all races and includes relatively many adults. The Census Bureau records a total population, in 1940 in Manhattan, of almost 1,900,000, of which 51 per cent were women; the same sex distribution holds true for the 1,580,000 white persons. Among the 298,000 Negroes, women totaled over 55 per cent, but for the other races, largely Asiatic, there were but 2,186 (15.6 per cent) women compared with 11,748 men. The preponderance of adults in the population is striking; slightly more than three-fourths of all persons on Manhattan Island were over 21 years of age. When it is recalled that at any given time New York City normally has about 500,000 visitors, most of whom are adults, and that the majority of them spend their time in Manhattan, the reservoir from which material for this study was collected is overwhelmingly composed of mature individuals. Also, during the working day, many adults from the other four boroughs of the city and from suburban communities add to the fixed population of Manhattan.

Diseases of the heart and aorta were first among the causes of death (45 per cent), and were succeeded, in order, by diseases of the respiratory tract (23 per cent), nervous system (18 per cent), digestive organs (6.2 per cent), urinary tract (almost 2 per cent), and genital apparatus (1.3 per cent). A

From the Office of the Chief Medical Examiner, New York, N. Y.
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miscellaneous group accounted for 4.4 per cent of the deaths, of which three-fifths, during the period under discussion, represented estivo-autumnal malaria in drug addicts.

The role of coronary arteriosclerosis in this galaxy is best illustrated and emphasized by the fact that in almost one-third (30.4 per cent) of the entire series of 2,030 cases death was caused by that disease. There is much misunderstanding of the symptomatology and manner of death, in relation to the fatal lesions in this disease, which has been responsible for medicolegal confusion. Responsibility for the misunderstanding may be attributed in part to the lack of appropriate data from medicolegal authorities; a share in the culpability belongs to those clinicians who attempt to evaluate coronary artery disease, where there have been no premortem symptoms, on the basis of experience with the more common examples encountered in office and hospital practice. Pathologists are not without blame, for, like clinicians, they also have too readily analyzed their material with criteria gained from autopsies of patients dying after days or weeks in the hospital. It cannot be overemphasized that the problems confronting the medical examiner in sudden and unexpected natural death, of whatever cause, require standards of evaluation with which the clinician and hospital pathologist are not familiar. Any attempt by the latter to substitute their experience for that of the medical examiner may lead to erroneous conclusions, especially important when testimony is offered in both criminal and civil actions, and serve to confuse and mislead their legal confreres.

Before presenting the data on coronary artery sclerosis and the conclusions drawn from their study, it should be pointed out that the finding of a severe grade of sclerosis of the coronary arteries does not, per se, mean that such disease is the cause of death. Death should not be attributed to diseases of the coronary arteries without a complete study of the circumstances and a full autopsy, including examination of the brain, and, where necessary, chemical examination of organs. In the absence of significant changes in organs other than the heart, with chemical findings unrelated to the death, and with a review of the manner of death (not always available), death may be ascribed to coronary artery disease when such disease is present and in adequate degree. Failure to observe all these criteria will result only in mistaken diagnoses.

The only work now available on coronary artery disease as a cause of sudden and unexpected death in a comparable large urban civilian population is that of Hallermann,² whose monograph appeared in 1939. During a five-year-period (1931 to 1935) at the Berlin Institute for Legal and Social Medicine, there were 6,481 necropsies in the noncriminal ("aussergerichtlich") category. Omitting ninety-eight cases of syphilitic mesaortitis with coronary ostial obstruction and four of coronary embolism, there were 681 instances of coronary artery sclerosis, including its complications and sequelae; an incidence of 10.5 per cent of the entire material. This represents a superficially marked deviation from the 30.4 per cent (617 cases) in our total material of 2,030 autopsied cases. The discrepancy may be explained in part by several facts. First, Hallermann's cases were

gathered from all of Berlin, the population of which undoubtedly included relatively more persons under 21 years of age than does that of Manhattan. Second, more necropsies may have been performed in the noncoronary-disease age groups. Third, factors militating against the necropsy in American cities are, generally speaking, absent in Central European communities. The institution of the autopsy has been widely accepted abroad, and legal requirements facilitate greater ease in its performance; the advent of the Hitler regime during the period of Hallermann's study probably made popular objection to any action by the authorities, even in medicolegal matters, less articulate. Finally, since it is not so stated, the Berlin total of 6,481 autopsies probably included those conditions specifically left out of this study (alcoholism, drug addiction, and so forth).

The two studies do coincide, however, when deaths from coronary artery sclerosis are compared with those from all heart and vascular diseases. The New York figures are 617 of 912 cases, or 67.7 per cent, while those of Berlin² are 681 of 1,028, or 66.3 per cent.

Coronary artery disease as a cause of sudden death is almost exclusively a malady of white men; only 6 per cent (thirty-six cases) of the subjects were women and these were only of the white race. A single Asiatic and twenty-three Negroes (3.7 per cent) were found among the male subjects, thus making the white male contribution to coronary artery sclerosis slightly more than 90 per cent. There is a striking disparity between the 3.7 per cent of male Negro cases and the 14.5 per cent representing the proportion of the male population which they formed. The discrepancy remains great even if all of the visitors to Manhattan are considered as white, and as men, thus reducing the Negro male population to 9.4 per cent. Lest it be thought that there is a relative immunity of Negroes to sudden and unexpected death from cardiac disease, it may be pointed out that, of the forty-six cases of death attributed to obstruction of the coronary ostia in syphilitic aortitis, eighteen (39 per cent) or two and one-half times the expected percentage, were Negroes. Syphilitic aortitis, however, does not come within the scope of this paper.

Hallermann's report does not include racial analysis of his material; even before Hitler's advent to power, the Berlin population was composed almost exclusively of white persons. There is, however, a marked difference in the sex composition of the cases in the Berlin monograph and those reported here. In the former, almost one-fourth of the cases of coronary artery sclerosis are women, while the New York group has but 6 per cent. Unfortunately, Hallermann does not give any indication as to the distribution and composition of all cases of sudden and unexpected natural death, so that comparisons are difficult. The two cities do resemble each other in that those engaged in the more humble occupations contribute much of the material in the category under investigation.

How do the various age groups stand out in the apportionment of coronary artery disease? The following figures deal only with white men, who, as already stated, make up 90 per cent of the cases in this classification. Grouping is by half decades (Fig. 1), with no cases found in persons 19 years of age or under.

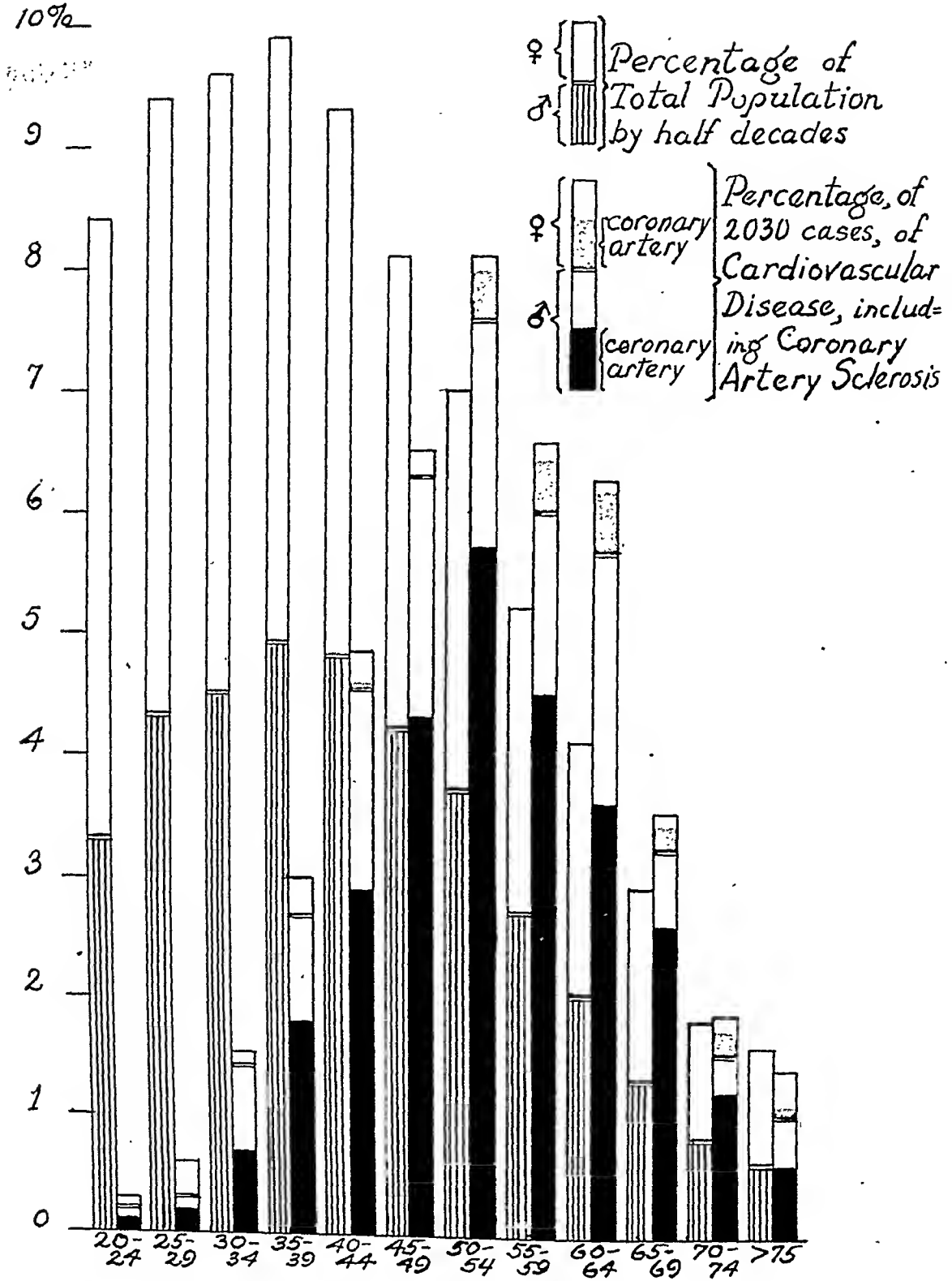


Fig. 1.—Graph showing percentage-age distribution, by half-decades, of (a) population of Borough of Manhattan, New York City, 1940, (b) cardiac and aortic disease among 2,030 cases of sudden and unexpected natural death (1937-1943), and (c) coronary artery sclerosis among the 2,030 cases.

As may be expected, the two half decades between 20 and 29 years provide but a fraction, 0.1 and 0.2 per cent, as compared with 3.3 and 4.3 per cent, the proportion of the white male population furnished by this age group. The next half decade, 30 to 34 years, still lags, but to a lesser degree; 0.7 per cent contrasted with its 4.5 per cent of male inhabitants. From 35 years of age onward, each group provides a greater contribution in proportion to its share of the population; thus, the age group 35 to 39 years provides 1.8 per cent as contrasted with 4.9 per cent of the population in this age range; 40 to 44 years provides 2.9 per cent, as compared with 4.8 per cent. From 45 years onward, each half decade contributes a greater percentage of sudden deaths than its share; 45 to 49 years provides 4.3 per cent as compared with 4.2 per cent of population; 50 to 54 years contributes 5.7 per cent compared with 3.7 per cent; 55 to 59 years, 4.5 per cent compared with 2.7 per cent; 60 to 64 years, 3.6 per cent compared with 2.0 per cent; 65 to 69 years, 2.6 per cent compared with 1.3 per cent population; 70 to 74 years, 1.2 per cent compared with 0.8 per cent; the group above 75 years contributes 0.6 per cent, equaling their percentage of the population. Thus, in this autopsied series, the incidence of coronary artery disease as a cause of sudden death in white men reaches a peak between 50 and 54 years and then gradually falls, its percentage remaining in excess of the percentage of the population that this age group furnishes. In summary, it can be stated that the thirty years between 44 and 74 have one and one-half times as many cases of sudden and unexpected death from coronary artery sclerosis and its complications and sequelae as would be expected from their contribution to the population.

It is difficult to compare Berlin with Manhattan Island in the age distribution of the cases. First, Hallermann's monograph does not include an age analysis of Berlin's population. Second, he does not give statistical data for all types of coronary artery sclerosis (thrombotic, nonthrombotic, with or without infarction, and so forth); he describes sclerosis, with or without old occlusion, and fibrosis of the myocardium for the period in question (1931 to 1935). As an appendix, Hallermann does give a brief summary of additional cases for 1936 to 1938. During these three years, the fourth to the sixth years under Nazi rule, there were about one-third more sudden and unexpected natural deaths from cardiovascular disease than during the preceding five years (two years under the Weimar Republic and three years under Hitler). The cases of coronary artery disease represented 66.3 per cent of cardiovascular deaths in the earlier, and almost the same proportion (62.5 per cent) in the later period, almost exactly corresponding to the New York values, as has already been noted. If a comparison is made of male deaths in New York with those in Berlin for the later period (1936 to 1938), there is a general trend toward higher values in the earlier age groups in New York; for example, 8.9 per cent as compared with 3.0 per cent in the fourth decade. The disparity sinks to 2:1 for the fifth decade, and practically disappears for the ages of 50 to 60 years. The two cities are virtually similar for the ages of 60 to 70 years, but for the next decade Berlin has twice the contribution of New York.

Of the 617 instances of coronary artery sclerosis, almost three-fourths (73.3 per cent) had no grossly demonstrable associated fresh thrombosis of the

vessels. This approximates the 95.3 and 80.2 per cent of the two Berlin periods. In most cases, atheromatosis with or without calcification had produced significant diminution of luminal caliber, so that, physiologically as well as anatomically, the effect was not different from that of old thrombosis. It should not be forgotten that functionally a narrowed sclerotic vessel, even without complete occlusion of the passage, may be inadequate in furnishing a satisfactory blood supply to the myocardium. From the statistical viewpoint, therefore, sudden unexpected natural death from coronary artery disease is best recorded simply as "coronary artery sclerosis."

Nonthrombotic sclerosis was free of fibrosis in 45 per cent and was associated with fibrosis in only 50 per cent, while infarction occurred in only 5 per cent. The Berlin statistics differ sharply from these values, since nonthrombotic sclerosis was associated with myocardial fibrosis in over 80 per cent of the cases, a difference in part attributable to the personal interpretation of the prosector as to what constitutes "fibrosis."

Slightly more than one-fourth of the instances of coronary artery sclerosis were complicated by fresh thrombosis. Seventy-five per cent (in the Berlin series, 60 per cent) of the cases with thrombosis showed infarction of the myocardium, both with and without antecedent fibrosis, in almost equal proportions.

In an attempt to obtain further clarification, more detailed information was obtained from the protocols of the cases studied during 1938 and 1939. Every profession and trade was represented, with the more humble callings expectedly predominating. In almost one-half of the cases (47 per cent) death took place in the street, or while at work, or in a public place; in an equally large proportion, the scene was the home or a hotel room. In the home, the bed (17 per cent) was as often the place of death as all other parts of the house combined (kitchen, bathroom, and so forth, 17 per cent). Those who died in hotels were generally found dead in bed, although not always following a night of rest and relaxation.

How much time elapses between onset of symptoms and death? Because a little more than one-third of the cases were found dead in bed, the time element is unknown in that large portion. Of the remaining slightly less than two-thirds, in which the period is known, almost 80 per cent died virtually instantly. Of the remainder, more lived beyond an hour than died in less than that time.

What relationship, if any, has the drinking of alcoholic liquors in the precipitation of death in coronary artery disease? In slightly less than 75 per cent of the autopsies, during the years under closer examination (1938 and 1939), alcohol determinations were done on liver or brain, chiefly the latter; four-fifths of these gave negative results. Of the remainder, 35 per cent gave results of 1 plus or a trace. It seems evident, then, that acute alcoholism plays no obvious role in the promotion of death in this disease.

It is sometimes asserted that coronary artery disability is associated with normal heart weight, and that cardiac enlargement is the exception. Let it be assumed that the upper limit of normal heart weight is 399 grams, a very generous allowance, and that the 25 per cent of cases in which the heart was not weighed

at necropsy also had hearts of normal size; yet 56 per cent of the series in the two years in question had hearts weighing 400 grams or more (Table I). This state was more striking in fibrotic hearts (82 per cent in nonthrombotic and 63 per cent in thrombotic disease). More than one-half of the enlarged hearts were heavier than 500 grams. It cannot be gainsaid that hypertension, which could not be assayed at necropsy, may have caused hypertrophy.

TABLE I. ANALYSIS OF 163 CASES OF CORONARY ARTERY SCLEROSIS (1938-1939) IN WHICH NATURAL DEATH WAS SUDDEN AND UNEXPECTED

EXTENT OF DISEASE					HEART WEIGHT IN GRAMS					
C	T	F	I	R	?	350	350-399	400-449	450-499	500
+					6	6	6	2	7	4
+		+			6	0	2	13	5	15
+			+		1	3	0	1	1	3
+				+	8	0	1	1	2	1
+	+				4	0	1	3	1	1
+	+		+		7	0	2	0	1	3
+	+	+			5	2	1	3	2	10
+	+	+	+		3	1	1	0	1	6
+	+			+	1	1	4	0	0	0
+	+	+		+	1	1	0	0	1	2
Total					42	14	18	23	21	45

C, coronary artery sclerosis; T, coronary artery thrombosis; F, fibrosis of myocardium; I, infarction of myocardium; and R, rupture of heart.

A brief description of the women with coronary artery disease may be in order. In our series, there was not a single case encountered until the age range, 40 to 44 years, was reached, when one subject was noted; none was found in cases between the ages of 45 and 49 years. In the ensuing half decades, the numbers were eight, eight, eleven, four, and four; there was only one case in subjects over 75 years of age. Although fatal coronary disease appears to manifest itself later in women than in men, as also found by Hallermann, the age range after fifty years furnishes more coronary artery disease in women than their proportion of the population.

SUMMARY

Among 2,030 cases of sudden and unexpected natural death autopsied over a six and one-half-year period in the Borough of Manhattan, New York City, in 45 per cent, death was attributed to diseases of the heart and aorta. Of these,

two-thirds (30.4 per cent of the 2,030 cases) were caused by coronary arteriosclerosis. This percentage of coronary artery disease in the cardiac and aortic group corresponds almost exactly with that reported from Berlin, Germany, over an eight-year period.

Sudden death from coronary artery sclerosis occurred most frequently in white men (90 per cent). The three decades between 44 and 74 years contributed one and one-half times their percentage share of the population, but sudden death from this disease began to appear in the third decade. Death took place under no specific circumstances.

In almost three-fourths (75.5 per cent) of the hearts, coronary artery sclerosis, and not fresh thrombosis, was responsible for vascular occlusion. In the remaining cases, a not always fresh thrombosis was encountered and an underlying sclerosis, usually of severe grade, was always present. It is incorrect to attribute death to coronary thrombosis without indicating the underlying primary sclerotic disease of the arteries.

Cardiac hypertrophy was found in 117 (66 per cent) of the 163 subjects whose deaths were analyzed during a two-year period. It was more prominent in the presence of myocardial fibrosis.

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AN AID FOR TAKING PRECORDIAL ELECTROCARDIOGRAMS

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THE long rubber belt usually supplied with electrocardiographs for taking precordial leads gives satisfactory results but is somewhat awkward to use. It is common practice, therefore, to dispense with this belt and have either the patient or the operator hold the exploring electrode in place. Because of unavoidable motion, however, this frequently results in some wandering of the baseline or other artifacts. The chest strap described in this communication combines simplicity and accuracy for taking precordial leads with the patient in the recumbent position.

The apparatus consists of two parts: (1) a transparent plastic strap weighted at both ends, which rests on the patient's chest and serves to hold the electrode in place; and (2) a transparent plastic block which replaces the usual electrode handle.

The chest strap is made of vinylite or similar flexible transparent plastic about 0.04 inch thick, 20 to 21 inches long, and 3 inches wide (Fig. 1). The vinylite used* was supplied in sheets roughly 18 by 48 inches in size, so that twelve strips 3 by 24 to 25 inches were obtained from each sheet.

Two weights, each between 2 and 3 ounces, are prepared. Brass plate about 2 1/2 inches x 1 1/2 inches x 1/8 inch is satisfactory. One is placed about 2 inches from each end of the plastic strap, the free ends are folded over and sealed so as to enclose these weights. Sealing can be done best by "electronic welding,"† but hand or machine stitching is satisfactory. No serviceable adhesive was found.

The plastic block can be made from Lucite or Plexiglass rod 1 inch to 1 1/4 inches in diameter, cut about 3/4 inch thick and polished for transparency. A hole is drilled in one of the flat surfaces to receive the central pin of the exploring electrode.

Method of Use.—The chest is marked and prepared with electrode jelly in, the usual fashion. With the patient in the recumbent or semirecumbent position one of the weighted ends of the chest strap is tucked under the left back and the strap draped across the thorax so that the width of the strap covers all of the

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*This is the type of vinylite which was used by the shoe industry during the war. The material was supplied for this study by the Phillips-Premier Corp., Boston, Mass.

†The "electronic welding" was done by the Victory Plastics Co., Hudson, Mass.

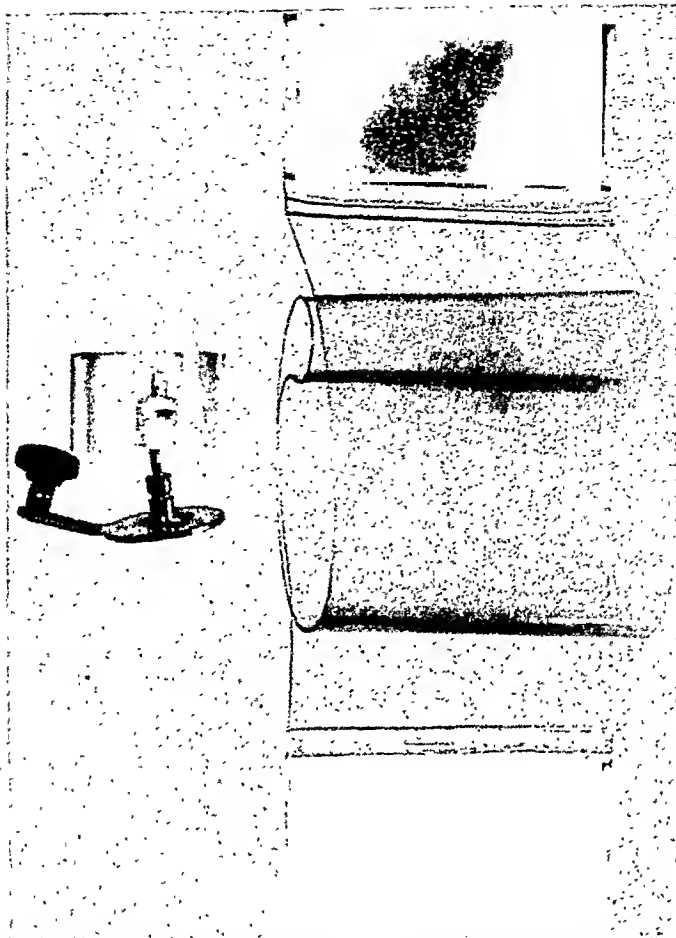


Fig. 1.—The two essential parts of the apparatus. On the right is shown the transparent plastic chest strap weighted at each end, and on the left, the plastic block fitted over the central pin of the chest electrode.

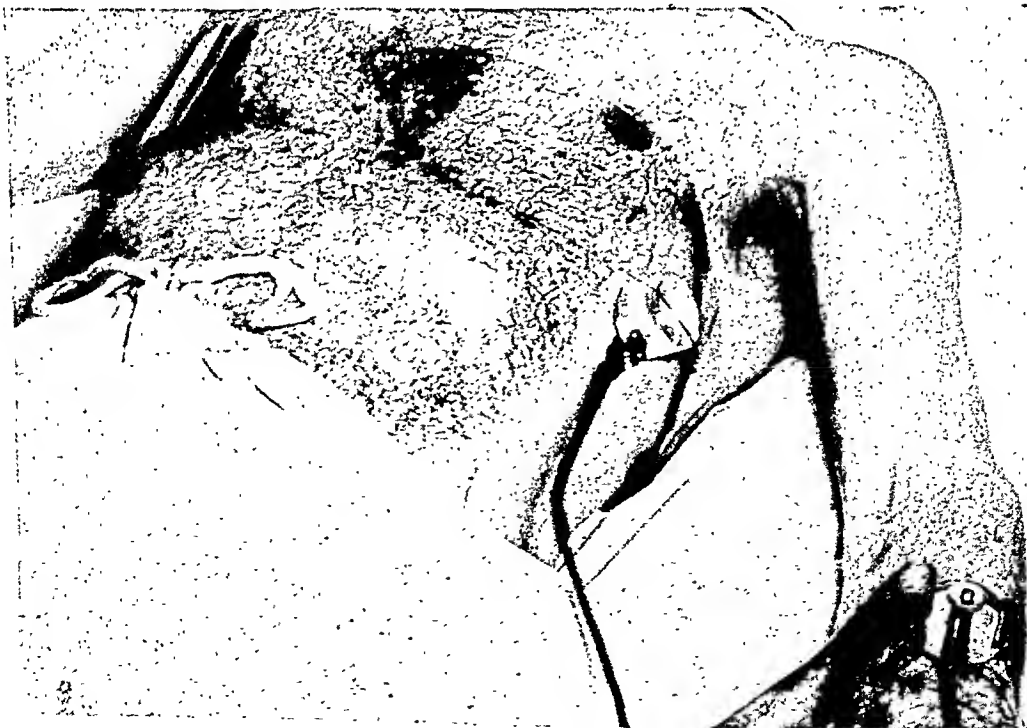


Fig. 2.—The chest strap and plastic block holding the electrode are shown applied to the chest.

marked positions and the free end lies on the right chest or in the right axilla. The block is fixed to the exploring electrode which is connected to the appropriate wire.

The free end of the strap is lifted momentarily, the electrode is placed in position, the strap is replaced, and the tracing is recorded (Fig. 2). This procedure is repeated for each precordial position desired.

The transparency of the strap and block makes it possible to see the location of the electrode at all times. When the electrode is in position, the strap rests snugly on the top of the block so as to clear the binding post and at the same time it hugs the chest and keeps the electrode in place. When taking electrocardiograms in Positions 5 and 6, especially if the breasts are pendulous, it may be advisable to place the left arm close to the side of the body. In Position 5 the electrode and block will rest just anterior to the left arm, while in Position 6 the arm will rest directly on the block.

A COMPARISON OF THE BLOOD PRESSURE IN THE LYING AND STANDING POSITIONS: A STUDY OF FIVE HUNDRED MEN AND FIVE HUNDRED WOMEN

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THE range of the normal blood pressure has been studied by several observers in the past so that the average blood pressure readings, at least for the sitting position, can be given with a high degree of accuracy.¹⁻³ The blood pressure has also been studied with the body in different positions.

The majority of these studies have been concerned with noting changes in the systolic blood pressure and heart rate as a means of determining physical fitness.⁴⁻⁷ The response of the heart rate to exercise and the time required for the heart rate to return to its previous level has been found to be the best index of physical fitness.⁸ The correlation of the change of blood pressure in different positions with physical fitness has been disappointing. Essential orthostatic hypotension has been well studied and is now considered a specific clinical entity which, at least in the minds of some investigators, is a lack of proper function of the sympathetic nervous system.⁹⁻¹¹ Postural hypertension has likewise been reported which might easily be the antithesis of postural hypotension, in which case overactivity of the sympathetic nervous system might well be the cause for such a reaction.¹² Renal blood flow has been found to be diminished in normal patients as well as in patients in whom a rise in blood pressure is associated with the erect posture.¹³⁻¹⁴

It seemed plausible, therefore, to study a large group of normal subjects to determine what happens to the blood pressure when one changes from a lying to a standing position. Such a study would tend to give clues as to the effect of the erect posture upon man; likewise, the effect of posture could be appraised as one of the factors in the etiology of early essential hypertension.

Man is one of the few animals who, undoubtedly, originally adapted to a four-legged position, has in the course of time changed his posture to that of the erect position and become the only biped of the primates.¹⁵ This, of course, has necessitated the development of certain compensatory mechanisms; this is particularly true in the cardiovascular system. The simple act of arising from a lying position and the ability to remain in the upright position calls upon the body to perform an unusual task to overcome the force of gravity. As Hill¹⁶ demonstrated in 1895, it is impossible to maintain most of the four-legged mammals in an upright position for any length of time without the animal dying as a

result, primarily, of circulatory insufficiency to the brain. This is due to the fact that the cardiovascular system is unable to compensate for the effect of gravity.

In man, evolution no doubt has presented us with certain constrictor mechanisms of the blood vessels of the legs and splanchnic area to prevent a fall of blood pressure when man assumes the upright position. This, of course, enables blood to reach the brain. Man is also, I believe, the only animal who in the absence of renal disease develops hypertension spontaneously.

METHOD OF STUDY

Five hundred men and five hundred women between the ages of 18 and 55 years were examined during a routine examination. All patients were white, and all European stocks were included in the study. The group included many young men who were considered essential for their work in the war effort. The examination was done at the time of a pre-employment or periodic physical examination and was carried out in an air-conditioned room at about 72°F., usually in the late morning or early afternoon. The blood pressure was first taken in the lying position after the patient had been supine for three to five minutes, or possibly longer. At least three readings were made by rapidly inflating the cuff above the systolic pressure and listening for the first and third auscultatory sounds as described by Korotkow, or until two consecutive readings were found to be the same. The patient was then asked to sit on the examining table and the remainder of the physical examination was completed. The patient then was asked to stand at ease upon the floor. The blood pressure and pulse were measured after the patient had been standing for at least three minutes. Three consecutive blood pressure readings were made in the same manner, or until two consecutive readings were found to be similar. The last reading was then taken.

There was encountered the usual number of patients who seemed slightly agitated for no other reason than that they were being examined by a physician. A few, of course, may have been slightly apprehensive as to whether they might pass the examination for employment or for flight duty. Every effort was made, however, to put the subject at ease.

The upper limits of normal for the blood pressure readings of this study were chosen as a systolic reading of 150 mm. Hg and a diastolic reading of 90 mm. of mercury.

The cuff was inflated as rapidly as possible to avoid undue congestion of the veins in the arm, which may have a tendency to raise the diastolic blood pressure. The arm was also held so that the brachial artery was at the level of the heart, since variation of the position of the arm, especially upon standing, makes a striking change at times in the diastolic reading. Differences of 10 mm. Hg in the diastolic reading were observed merely by letting the arm drop to the side and then determining the blood pressure; with the arm at the side, the brachial artery is dependent to the heart by 10 to 15 centimeters.

Some readings were made by taking the diastolic reading first. The cuff was inflated rapidly to about 10 mm. Hg above the estimated diastolic pressure. The cuff was deflated and the diastolic reading was made. The blood pressure was then determined in the more conventional style of taking the systolic reading first and then the diastolic reading. No appreciable difference in the diastolic reading was noted, although at times the diastolic reading seemed more distinct when the diastolic reading was made first.

RESULTS AND DISCUSSION

The pertinent data from this study are presented in Tables I, II, and III. The abnormally elevated blood pressure readings were divided into seven groups, distinction being made between systolic and diastolic hypertension and as to whether the abnormality occurred in the lying or standing position, or both. The composition of the seven groups is shown in Table I.

The incidence of hypertension, diastolic and systolic, in the lying and standing positions was about equal for the groups of men and women and averaged 3.4 per cent. The incidence of diastolic hypertension alone in the lying and standing positions was even higher, and the average for the two groups was 3.9 per cent. It is interesting that nearly twice as many men demonstrated a diastolic hypertension as compared with women. It is appreciated, of course, that the

TABLE I. THE INCIDENCE OF VARIOUS TYPES OF HYPERTENSION IN THIS STUDY WITH A COMPARISON OF THE MEN WITH THE WOMEN

GROUP		MEN (PER CENT)	WOMEN (PER CENT)	AVERAGE (PER CENT)
1	Diastolic and systolic hypertension, lying and standing	3.0	3.6	3.4
2	Diastolic hypertension, lying and standing	5.0	2.8	3.9
3	Diastolic hypertension, lying only	0.8	0.2	.5
4	Diastolic hypertension, standing only	6.4	1.8	4.1
5	Systolic hypertension, lying and standing	0.4	0.4	0.4
6	Systolic hypertension, lying only	0.2	0.6	0.4
7	Systolic hypertension, standing only	.00	0.2	0.1

TABLE II. THE BEHAVIOR OF BOTH DIASTOLIC AND SYSTOLIC BLOOD PRESSURE READINGS UPON CHANGE IN POSTURE

	MEN	WOMEN	AVERAGE
Diastolic pressure increased 4 mm. or more	53%	44%	48.3%
Diastolic pressure decreased 4 mm. or more	14%	9.8%	12.0%
No appreciable change (less than 4 mm.)	33%	46.2%	39.7%
Systolic pressure increased 10 mm. or more	4.2%	3.2%	3.7%
Systolic pressure decreased 10 mm. or more	36.8%	28.8%	32.8%
No appreciable change (less than 10 mm.)	59%	68%	63.5%
Average age (years)	33.9	32.5	33.2

TABLE III. CHANGES IN THE PULSE RATE UPON CHANGE IN POSITION IN THIS STUDY. CHANGES OF AT LEAST TWO BEATS PER MINUTE OR MORE WERE CONSIDERED SIGNIFICANT

	MEN	WOMEN	AVERAGE
Average pulse rate, lying	77.3	79.3	78.3
Average pulse rate, standing	89.6	91.0	90.3
Range of pulse rate, lying	52 to 125	54 to 118	
Range of pulse rate, standing	54 to 140	60 to 148	
Average increase in pulse rate per minute on standing	13.3	13.0	13.2
Range of increase in pulse rate on standing	2 to 44	2 to 42	
Increase in pulse rate on standing	96%	94.6%	95.3%
No change in pulse rate on standing	2.4%	3.2%	2.8%
Decrease in pulse rate on standing	1.6	1.8	1.7

incidence of diastolic hypertension alone would not have been as great had the upper limit of normal for systolic blood pressure been reduced from 150 to 140 mm. of mercury. However, it should be emphasized that the diastolic reading is of much more importance than the systolic reading from the standpoint of estimating peripheral resistance, which, of course, is the important determination in hypertension. As a matter of fact, the systolic blood pressure can be disregarded to advantage in clinical medicine, at least in the study of hypertension. The practice of reporting the diastolic blood pressure and the pulse pressure would give the same information and would tend to encourage thought along more physiologic lines.

Comparison of Groups 3 and 4 of this study amply demonstrates the effect of posture upon the diastolic blood pressure, at least in those persons whose diastolic pressure hovered around 90. The occurrence of an abnormal diastolic blood pressure reading only in the standing position, as compared with the lying position, was found eight times more frequently in men and nine times more frequently in women. Comparison of the men and women in Group 4 is also of interest, as it demonstrates that diastolic hypertension, only in the standing position, was almost four times as common in the men as in the women in this group. The average of the two groups, men and women, is 4.1 per cent and even exceeds the figure for Group 2 in this study.

The incidence of what is commonly called essential hypertension (Group 1 in this study) is a rather low figure of 3.4 per cent. However, if one combines Groups 1, 2, and 4, which gives the percentage of elevated diastolic blood pressures in the standing position, the incidence is remarkably increased to 11.4 per cent. It is appreciated that certainly not all the patients in Groups 2 and 4 will eventually develop essential hypertension. Certainly the initial blood pressure reading on a patient is frequently higher than most subsequent readings, and not infrequently even exceeds the highest blood pressure reading which can be obtained with such a test as the cold pressure test. This, of course, is a nervous phenomenon resulting from the patient's nervous tension at the time of the physical examination, but it is fitting to use this bit of information in recognizing this

group of cases as patients with transient hypertension. If this is true, there seems good evidence to indicate that a higher percentage of these subjects will later develop hypertension as compared with the patients whose blood pressure remains the same or falls during such an observation.

It is of considerable importance, therefore, to observe patients with borderline blood pressure readings, particularly diastolic readings which hover about 90 mm. Hg in both the lying and standing positions, to determine the response of the diastolic pressure to the change in position. In fact, standing, alone, may be one pressor test, particularly at the time of the initial examination of the patient where both the standing position and the nervous tension of the examination will very likely produce a maximum response of the diastolic reading.

Groups 5, 6, and 7 of this study indicate the relative infrequency of systolic hypertension alone in the absence of some elevation of the diastolic pressure. The fact that the average age of the whole group was 33.2 years and that none of the patients was over 55 years of age excludes those elderly patients who have systolic hypertension as a result of an inelastic, sclerotic aorta.

From Table II one can obtain some idea as to the change in the systolic and diastolic blood pressure readings upon change of posture. A change of 4.0 mm. Hg or more in the diastolic blood pressure readings or a change of 10 mm. Hg or more in the systolic reading were arbitrarily taken as being of some significance. It is quite apparent that the diastolic reading increased approximately four times as frequently as it decreased. In approximately 40 per cent there was no change; the reverse was true of the systolic blood pressure reading. In over 60 per cent of the cases there was no appreciable change. In the majority of the remaining cases (33 per cent), however, there was a fall of the systolic pressure of 10 mm. or more. The tendency, therefore, was for the pulse pressure to decrease at the expense of a decrease in the systolic pressure, as well as of a rise in the diastolic pressure. It should be emphasized that there were cases in which there was no appreciable change of either systolic or diastolic blood pressure and a few cases in which both pressures decreased. The degree of change together with the frequency is illustrated in Fig. 1.

Table III gives the results of the observations of the pulse rate during this study. The average pulse rate for the whole group while lying was 78.3 per minute. Upon standing the average pulse rate rose to 90, and in each position the difference between the groups of men and women was probably not significant. The resting pulse rate, lying, of 78 is higher than the average basal resting pulse rate, which indicates that a certain amount of nervous tension was associated with undergoing a physical examination. It is also apparent that under the conditions of this study practically all of the pulse rates increased upon standing, since 95 per cent of the group showed this increase. The average increase was essentially the same in both the groups of men and women and amounted to 13.2 beats per minute.

Some of the patients who had either diastolic hypertension lying and standing or diastolic hypertension only while standing (Groups 2 and 4 of this study)

did show a considerably faster pulse rate than normal, but others demonstrated a perfectly normal pulse rate. However, the average for the pulse rate of Groups 2 and 4 of this study was about 96 beats per minute as contrasted with the overall average of 90 beats per minute. Although this difference is slight, it is probably significant.

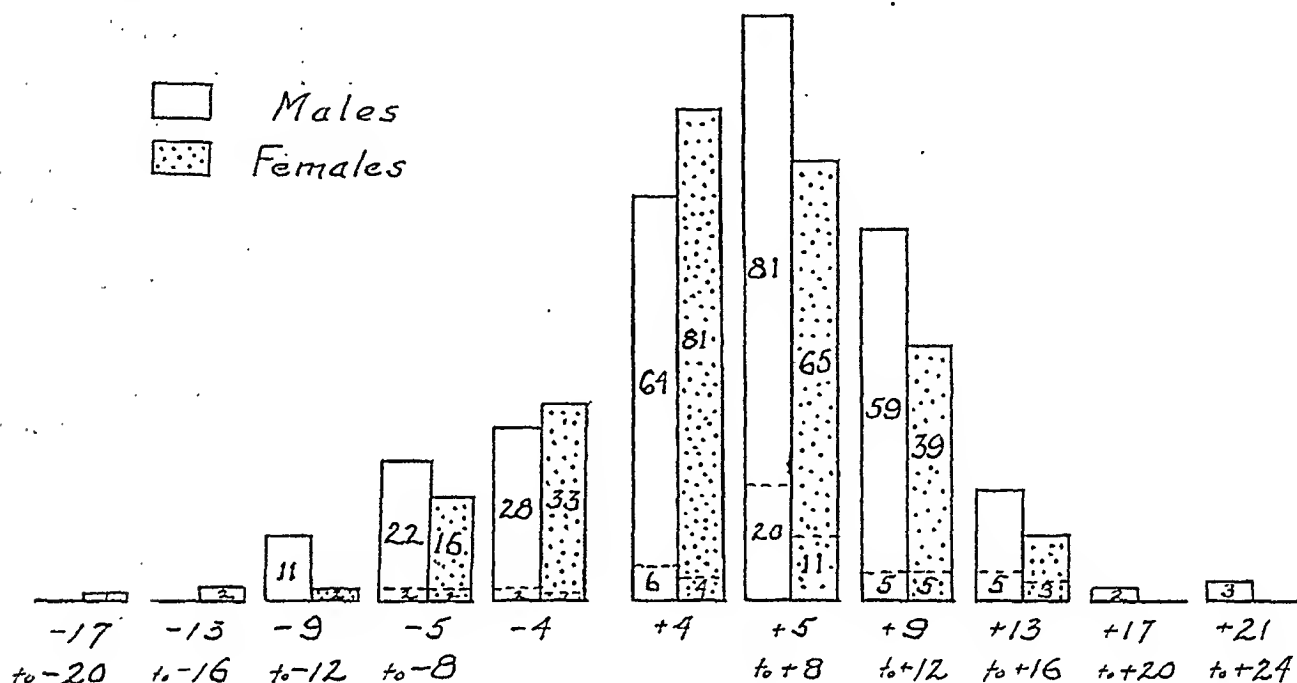


Fig. 1.—The degree and range of change in the diastolic blood pressure readings with change in posture is presented. The cases with a less than 4 mm. change are not represented. The areas below the dotted lines indicate those patients with hypertension in one or both positions. The relative shift to the right in the figure is apparent. The figures represent the number of cases.

The position of the arm is of considerable importance when taking the blood pressure, especially in the standing position.¹⁹⁻²¹ The blood pressure, particularly the diastolic reading, has a tendency to increase with dependency and to decrease as the arm is raised above the heart. In the horizontal plane, the position of the arm does not seem to have an appreciable effect upon the diastolic blood pressure.²² One might expect that dropping the brachial artery about 10 cm. below the heart would increase the pressure in the artery approximately 10 mm. Hg since the weight of a 10 cm. column of blood is approximately equal to the weight of a 10 mm. column of mercury, the specific gravity of blood being 1.06 and that of mercury 13.6.

In 1904 Erlanger and Hooker²³ published a rather comprehensive study of the effect of change of posture upon one normal individual and demonstrated that the vasoconstrictor element on standing could be eliminated by immersing the body when erect in water. They also demonstrated that immersion of the body in cold water had a pressor effect upon the blood pressure and that the diastolic blood pressure is nearer the mean blood pressure than is the systolic blood pressure. Wald and associates,²⁴ have called attention to the changes in blood pressure during the first minute of standing. After the first minute, they

found no appreciable change, indicating that the adjustment to standing is quite rapid.

During the course of this study a moderate number of Negroes were examined and the blood pressures in the lying and standing positions were compared. The number, however, proved too small to be of any significance. The comparison between white people and Negroes would be of interest because of the observation that hypertension seems to be more frequent in Negroes. Then, too, a follow-up study in ten or twenty years of the patients in this report with borderline blood pressure readings, particularly in the standing position, would be of the utmost importance in evaluating the role of posture as a factor in the etiology of essential hypertension.

The possible relationship between the vertical stance of man and essential hypertension is an interesting one. Since the diastolic blood pressure reading gives the best index we have of peripheral resistance, it is pertinent to know under what conditions in man the diastolic blood pressure is enhanced. It is true that many human beings are able to make the compensatory adjustment to the erect posture without appreciable change in the diastolic blood pressure; in fact, there are some subjects in whom the diastolic pressure falls somewhat upon standing. In about one-half of the individuals in this study the diastolic pressure increased upon standing. Since man spends about one-half to two-thirds of his time in the erect or semierect position each day, it is conceivable that over a period of years the increment in the diastolic blood pressure in the vertical stance is an important factor in the gradual increase in peripheral resistance. Nervous stimuli, pain, and cold are also important factors which will raise the diastolic blood pressure of man. It may be that a combination of several factors results in gradually raising the peripheral resistance to the blood flow in man and it seems logical to assume that the vertical stance is one of these factors. Perhaps this is the price that a certain percentage of human subjects have to pay for being bipeds.

If lumbodorsal sympathectomy produces essentially a postural hypotension, one might expect men to have a greater chance of benefit than women, since from this study it would seem that the diastolic blood pressure is more frequently raised in men than in women upon standing. This has not, however, been the experience with sympathectomy for hypertension, in which case women seem to have better results than men.

SUMMARY

1. Observations were made on 1,000 healthy individuals (500 men and 500 women) between the ages of 21 and 55 years with respect to the change in blood pressure in the lying and standing positions. The incidence of both diastolic and systolic hypertension, lying and standing, was found to be 3.4 per cent.

2. The presence of diastolic hypertension (lying and standing) was found, however, to be more common than essential hypertension, the incidence being

3.9 per cent in this study. Nearly twice as many men as women were found to demonstrate diastolic hypertension.

3. The presence of diastolic hypertension in the standing position alone was found to be even more frequent, averaging 4.1 per cent with a sex ratio of about 3.5 men to one woman.

4. The possible role of the erect posture as one of the factors in essential hypertension is considered.

Acknowledgment is made to Dr. Paul D. White for helpful criticisms and suggestions.

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Clinical Reports

MYOCARDIAL INFARCTION IN A TWELVE-YEAR-OLD BOY WITH DIABETES

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A REVIEW of recent literature emphasizes that more and more frequently coronary disease is being recognized and diagnosed in young adults.¹⁻⁸ However, coronary occlusive disease can also occur in infants and children, as Stryker points out in a review of the subject.⁹ Because of the relative rarity of such lesions, the clinical history of myocardial infarction in a 12-year-old boy with diabetes mellitus is reported.

CASE REPORT

H. R., a white boy 12 years of age, was admitted to the Wayne County General Hospital and Infirmary on Sept. 17, 1945, in a semicomatose state. The only history available was that he had been a known diabetic since the age of 2 years. His diet was uncontrolled, except for the restriction of sweets, and he took 15 units of protamine zinc insulin before breakfast. For a few days prior to admission he had been sneezing and coughing, and on the day of admission he complained of a pressure sensation across the chest.

A more detailed history was obtained later which revealed that throughout childhood he had had frequent head colds, tonsillitis, and pharyngitis. Every since the discovery of the diabetes, he had migratory joint pains and frequent epistaxes. From 1940 to 1943, he had repeated hospitalizations for the regulation of his diabetes. In 1943, he had a mild attack of scarlet fever but recovered without complications. For the past one to two years, the parents had noted dyspnea on mild exertion and slight ankle edema. On Sept. 1, 1945, after eating a good meal, the child suddenly experienced severe, constricting pain under the middle of the sternum and had severe dyspnea and orthopnea.

The family history was unremarkable except for the death of two siblings, one being stillborn and the other dying on the first day of life. Three other siblings were living and well. A paternal cousin had diabetes mellitus.

At the time of admission, the temperature was 97.6° F., the respirations were 30 per minute, and the pulse rate was 130 per minute. The systolic blood pressure was 135 mm. Hg; the diastolic pressure was unobtainable. The patient was a pale, very small but fairly well-proportioned boy of 12 years, conscious but lethargic. His breathing was Kussmaul in type. The pupils were irregular, round, and equal. Funduscopy was negative. The pharynx was injected and the tonsils were large and slightly reddened. The chest was clear to percussion and auscultation. The heart was enlarged to the left and the left border of cardiac dullness was 2.5 cm. beyond the midclavicular

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line in the fifth intercostal space. The aortic second sound was louder than the pulmonic second sound. No cardiac murmurs were heard and normal sinus rhythm was present. There was an increased area of gastric tympany.

On admission, the blood sugar was 600 mg. per cent and the nonprotein nitrogen was 60 mg. per cent. The carbon dioxide combining power was 7 volumes per cent. The urine showed 4 plus sugar and the presence of acetone. The differential blood count showed 58 polymorphonuclear leucocytes, of which 31 were filamented and 27 nonfilamented, 29 lymphocytes, 9 monocytes, 1 basophil, 2 metamyelocytes, and 1 myelocyte. There was toxic granulation of the polymorphonuclear leucocytes.

Gastric aspiration done on admission recovered 1,500 c.c. of fluid. In the first six hours of treatment the child received 3,000 c.c. of intravenous fluid containing 250 grams of glucose and 135 units of crystalline zinc insulin. During this period, the carbon dioxide combining power rose from 7 volumes per cent to 46 volumes per cent and at the end of eighteen hours, only a trace of acetone remained in the urine (Table I).

TABLE I. LABORATORY FINDINGS

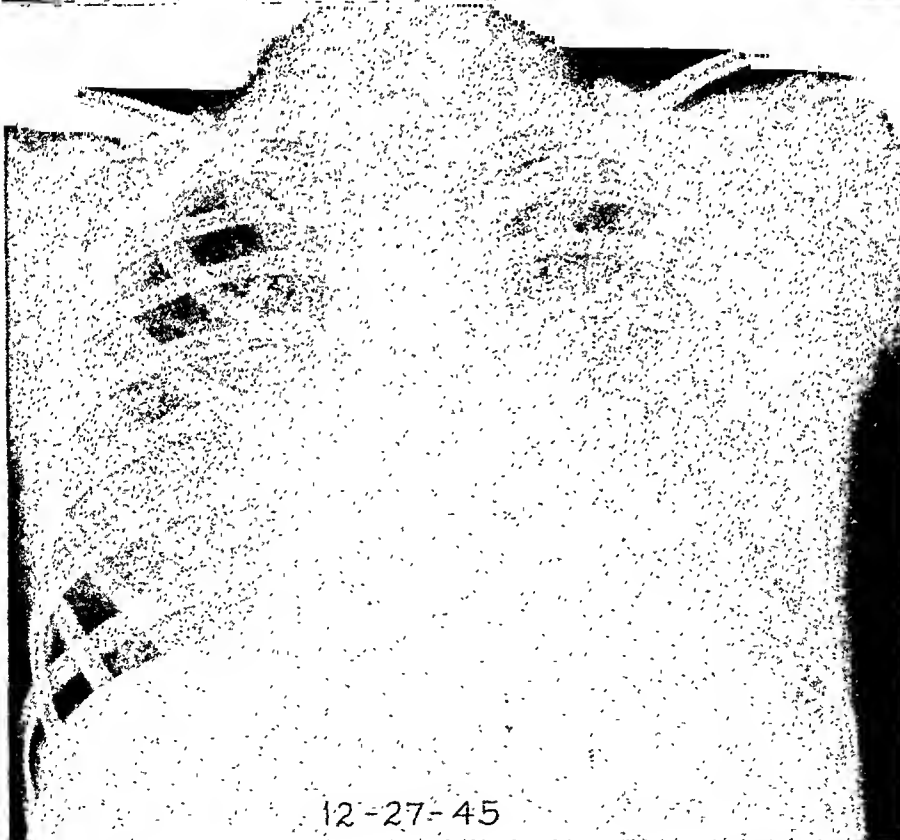
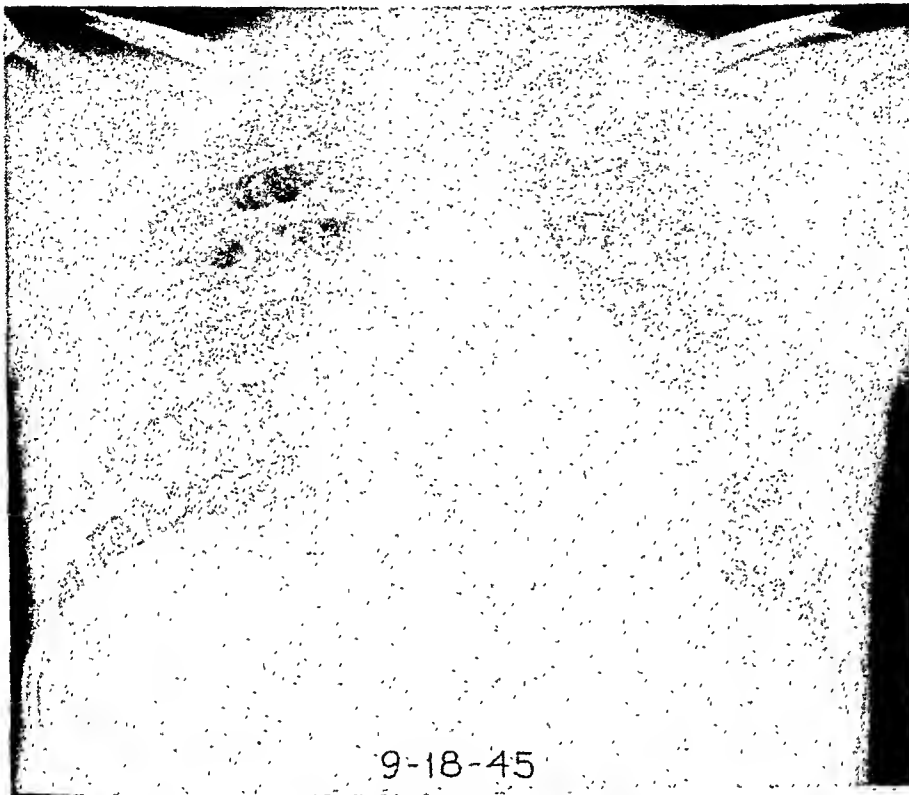
Urinalyses

DATE	SP. GR.	ALB.	SUGAR	ACETONE	MICROSCOPIC
9/17/45	—	++++	Tr.	+	Occ. WBC. No organisms in stained sediment
9/27/45	1034	+	++++	0	Many gram-neg. bacilli, few micrococci and gram-pos. diplococci
10/ 6/45	1030	+++	0	0	2-3 hyaline casts; 4-6 WBC.
10/ 8/45	1019	0	0	0	Neg. except for few gram-pos. cocci
12/11/45	1022	++	0	0	4-6 hyaline casts, 3-4 WBC, 1-2 RBC
12/15/45	1011	+	0	0	3-4 WBC, 1-2 RBC
12/19/45	1028	++	++++	0	3-4 hyaline casts, 4-8 WBC, 1-2 RBC.
2/ 6/46*	1013	+++			Occ. WBC and RBC. Numerous granular and occ. hyaline casts

During this same period, the temperature rose from 97.6° F. rectally to 102.4° F., and the pharynx became red and edematous. The chest was clear to percussion and auscultation and there was no edema peripherally. The blood pressure fell to 90/55. A transfusion of 200 c.c. of whole blood was given and intramuscular penicillin in doses of 20,000 units every three hours was started. The following day, a roentgenogram of the chest showed early bronchopneumonia, pleurisy on the right, and an enlarged heart (Fig. 1). At this time, the patient complained of substernal pain on deep inspiration.

During the next week, the temperature continued elevated. Râles and dullness at the bases of both lungs persisted. There was occasional acetonuria and persistent glycosuria. Therefore, efforts were made to regulate the diabetes by small daily doses of protamine zinc insulin and crystalline insulin administered before meals according to the reaction of the urine.

A.



B.

Fig. 1.—A, Roentgenogram of chest showing pleurisy on right, early bronchopneumonia and enlarged heart. B, Roentgenogram of chest suggestive of passive congestion of both lung fields. Pleura thickened at both margins.

Blood Counts

DATE	HB. GMS.	WBC	DIFFERENTIAL							
			PMN	F	NF	L	M	B	E	
9/17/45	15	49,100	58	31	27	29	9	1		1 myelocyte 2 metamyelocytes
9/27/45	12.7	11,550	72	65	7	19	8			
10/10/45	13.5	9,200								
10/29/45	13	5,200	51	51	0	29	15		5	
12/ 7/45	13	9,150	65	63	2	32	3			
2/ 6/46*	11	15,150	69	61	8	27	2	2		

Blood Chemistry

DATE	GLUCOSE	NPN	CHOLESTEROL	CO ₂	SERUM PROTEIN
9/17/45 11:00 A.M.	600	60	190	7	5.3
1:30 P.M.	695			21	
8:30 P.M.	62			77	
9/29/45		32			
10/ 2/45					
10/ 8/45	170	69			
10/11/45	56	41			
11/ 2/45	323				
12/ 7/45	120	50			
12/ 8/45	37	34		60	Albumin 2.5, globulin 2.9
12/15/45	250				
12/21/45	135				

*Information from records at Detroit Receiving Hospital.

On Sept. 15, 1945, the râles had disappeared from both lungs, but a pericardial friction rub developed at the cardiac apex and a reduplicated second sound was noted at the base of the heart. The legs were markedly edematous. An electrocardiogram taken the following day showed tachycardia and evidence of an extensive anterior myocardial infarct. See Fig. 2 for serial changes.

On Sept. 26, 1945, a roentgenogram of the chest was interpreted as showing congestion of the lung fields with a slight effusion present on the right side. The cardiac configuration was suggestive of mitral disease. The friction rub had disappeared. The patient was digitalized. Two days later, the right chest showed definite physical signs of pleural fluid and the liver was felt three fingerbreadths below the right costal margin.

Because signs of pleural fluid persisted, a thoracentesis was performed on Oct. 2, 1945, and 150 c.c. of serous fluid was removed from the right pleural cavity. Its specific gravity was 1.010 and culture and smear were negative for any organisms. At that time, a roentgenogram was taken which indicated that the greatest transverse diameter of the heart had increased 1.5 centimeters. The possibility of a pericardial effusion was considered. Because of persisting gener-

alized edema, 0.5 c.c. of Mercurhydrin was given intramuscularly on Oct. 6, 1945, which caused a satisfactory diuresis with a diminution of the ascites and the pleural effusion. The ankle edema disappeared and for the first time the child was afebrile.

Although the urine was kept acetone-free, the diabetes was poorly stabilized; the fasting blood sugars varied from 56 mg. per cent to 323 mg. per cent. On Nov. 17, 1945, the patient was discharged with instructions to eat a salt-free weighed diet and to take 20 units of protamine zinc insulin and 20 units of crystalline zinc insulin before breakfast, 5 units of crystalline zinc insulin before lunch, and 15 units of crystalline zinc insulin before supper.

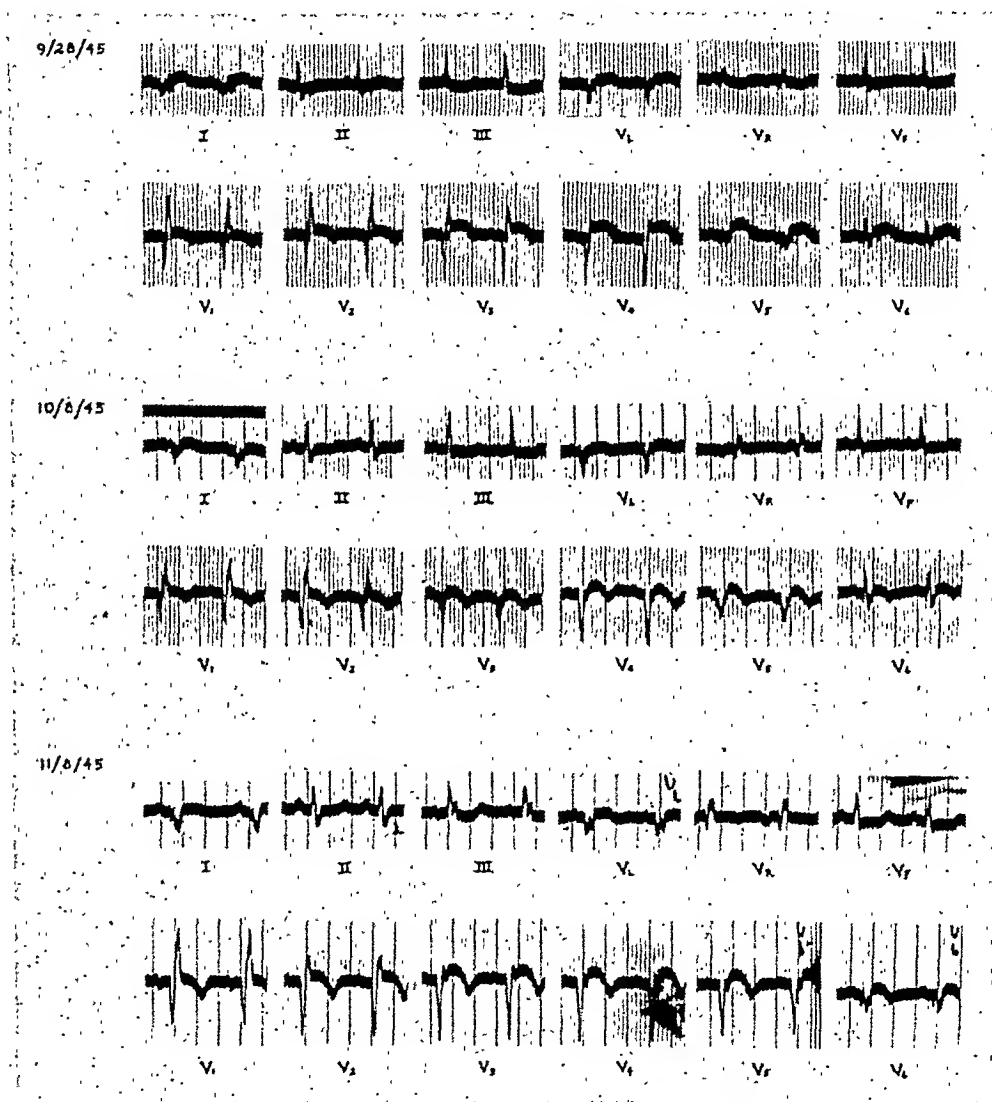


Fig. 2.—Electrocardiograms showing the standard, precordial, and extremity leads. The QRS and T-wave changes suggesting infarction are most prominent in the chest leads.

On Nov. 29, 1945, the patient was seen in the outpatient clinic of this hospital where it was learned that because his appetite had failed immediately upon going home, the parents had attempted the regulation of the insulin dosage. His fasting blood sugar on that day was 133 mg. per cent. On examination, the left heart border was at the anterior axillary line and a systolic murmur and a split second sound were heard over the entire precordium, but best heard at the apex. The chest was free of râles; the liver was slightly enlarged, but no edema was noted.

On Dec. 6, 1945, the patient was readmitted to this hospital with edema of the entire body and ascites which first became evident on Dec. 1, 1945, following a severe insulin reaction. The essential physical findings at that time were: retinal edema, crystalline retinal exudates, and an

increased arteriovenous ratio. There was decreased resonance at both lung bases, with no change in the breath sounds. There was marked ascites and a 4 cm. enlargement of the liver by ballottement. The patient had bilateral costovertebral angle tenderness with marked edema of the penis, scrotum, and lower extremities. The fasting blood sugar was 180 mg. per cent and the nonprotein nitrogen was 50 mg. per cent.

During the next week, the diabetes was well controlled on a salt-free diet plus crystalline zinc insulin before meals. Because of marked respiratory distress and a rapid heart rate, on Dec. 11, 1945, the patient was redigitalized, given 0.5 c.c. of Mercurhydrin intramuscularly, and oxygen. From Dec. 12, 1945, on, the patient had periods of delirium which came on at about 6:30 P. M. each day. The insulin dosage was reduced with some improvement in the symptoms but the patient continued to complain nightly of substernal and left shoulder pain. On Dec. 29, 1945, the parents removed the child from the hospital against medical advice.

On Feb. 2, 1946, the patient entered The Detroit Receiving Hospital.* Since leaving Wayne County General Hospital and Infirmary, there had been a gradual increase in anasarca until one week before admission, when it had increased rapidly. This was somewhat relieved by an injection given by a local physician which caused marked diuresis. During the week preceding his final hospital admission, he also had an upper respiratory infection. On Feb. 1, 1946, he had constant sharp precordial pain which radiated down the left arm. On admission to The Detroit Receiving Hospital, the physical examination was essentially the same as previously described, except for the following: the fundal vessels showed an arteriovenous ratio of 1:2; there was arteriolar spasm but no sclerotic changes. There were small linear and round hemorrhages, and retinal edema was marked. The chest showed decreased tactile fremitus in the right axilla and decreased resonance to percussion throughout. The cardiac findings were as previously described. The blood pressure was 135/100.

For the next two to three days, following mercurial diuresis, he seemed to improve but on Feb. 6, 1946, he coughed up a small amount of bright red sputum. Inspiratory and expiratory rales were heard in the right midaxilla and at the right lung base. A roentgenogram showed "diffuse soft peribronchial reaction throughout lung fields with consolidation of the right upper lobe. There is minimal pleural thickening of right lateral chest wall." Intramuscular penicillin therapy was begun but the patient expired on Feb. 6, 1946. Permission for autopsy was refused.

The final diagnoses were (1) terminal bronchopneumonia, (2) cardiac decompensation, (3) old anterior myocardial infarction, (4) diabetes mellitus, and (5) chronic glomerulonephritis.

SUMMARY

A case of myocardial infarction occurring in a 12-year-old boy with diabetes mellitus is reported.

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SUCCESSFUL TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH STREPTOMYCIN

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REPORTS of the successful use of streptomycin in the treatment of subacute bacterial endocarditis have appeared in the literature, but they are rare.¹ Priest and McGee² were successful with the drug in eradicating the endocardial infection in two patients but failed in a third. The infecting organism in all three was a pleomorphic streptococcus, the earliest and most pleomorphic forms being gram negative and the older forms, which appeared as pairs and short chains of cocci, being gram positive. Later, however, after the culture had been frozen, the organism grew as a typical *Streptococcus viridans* (type not specified) with a green hemolytic zone. In all three cases, the organism appeared to be highly resistant to penicillin but sensitive to streptomycin. In one, the drug could not be obtained until the last five days of the patient's illness, but at autopsy no bacteria could be demonstrated on the scattered remnants of fibrin on the valves involved.

Cady and Allen,³ and Cady and Hunter⁴ reported the unsuccessful treatment of subacute bacterial endocarditis due to *Streptococcus viridans* fecalis with streptomycin. That the drug can be used effectively in this type of infection is illustrated by the following case report.

REPORT OF CASE

M. S., a 50-year-old white housewife, was admitted to the hospital Nov. 11, 1946, complaining of weakness and fever. She denied any serious illnesses in the past, except the usual childhood diseases, and there was no history suggestive of any part of the rheumatic diathesis. She felt that she had enjoyed unusually good health all her life until ten weeks prior to admission when she suddenly became ill with fever, chills, sore throat, and generalized aching. Her family physician treated her symptomatically for influenza for one week. Fever had subsided at the end of a week, but she felt unusually weak, and after several days she discovered that she was running a low-grade, daily afternoon temperature elevation. During the ensuing weeks she became progressively weaker; fever became continuous, she suffered from drenching night sweats, and lost about twenty pounds in weight. Three weeks before admission she had taken two tablets of one of the sulfonamides every four hours for four days without noticeable improvement in her fever or general condition. At this time she noticed rapidly progressive exertional dyspnea which was promptly followed by moderate orthopnea, but there had been no precordial pain, palpitation, paroxysmal dyspnea, or edema. She began to suffer from occasional bouts of moderate epistaxis, and on several occasions she noticed the appearance of subcutaneous bleeding without known trauma. The patient's vision had been blurred for several weeks, and she complained also of floating scotomata. Review of systems, past history, and family history were irrelevant.

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Physical examination revealed a thin, pale, white woman of stated age lying quietly in a semi-Fowler position and appearing chronically ill. The skin was dry and essentially clear. The tips of several of the fingers were tender, but no splinter hemorrhages were seen, although several days later they were abundant. Petechial hemorrhages were present on the soft palate and in the left conjunctival sac, but none were found on the skin. The head was essentially negative. The pupils were equal, regular, and normally reactive. The nerve heads were well outlined and the vascular pattern was essentially normal, but there were numerous old and fresh round, flame, and crescent-shaped hemorrhages in both eyes. The ears, nose, and throat were essentially normal, and the sinuses transilluminated well. A few lower remaining teeth appeared in good condition. The tongue was normal and the pharynx clean.

The peripheral nodes were not remarkable except for a few small, shotty nodes beneath the angle of the jaw bilaterally. The trachea was in the mid-line; there was no tug, and the thyroid was not palpably enlarged.

The chest expanded equally and symmetrically. The percussion note was resonant throughout and the breath sounds were soft and vesicular everywhere. No râles, rhonchi, or friction rubs were heard. The heart apparently was slightly enlarged to the left but the aorta did not seem to be uncoiled or dilated. The waistline was not obliterated to percussion. There was considerable precordial activity and a suggestion of a systolic thrill at the apex. The rate was 110 per minute and the rhythm was regular. There was a harsh, Grade 2 systolic murmur heard best at the apex but transmitted well over the entire precordium and heard easily in the axilla and at the angle of the left scapula. The first sound at the apex was not accentuated. The pulmonic and aortic second sounds were equal and neither was appreciably increased. There was no gallop or friction. Diastolic murmurs were not heard at this time in any position. The blood pressure was 140/70 in both arms. The peripheral vessels were not appreciably thickened and the venous pressure appeared normal clinically.

The abdomen was soft and scaphoid. There was no tenderness. The liver, kidneys, and masses could not be felt, and attempts to palpate the spleen were unsuccessful. There were no costovertebral angle tenderness, sacral edema, or hernias. Pelvic examination revealed a marital introitus with good support. The pelvic examination was negative.

The extremities were essentially negative except for finger tenderness as already noted. Neurological examination was essentially normal. All deep and superficial reflexes were generally hyperactive.

Repeated examinations of the urine were normal except for occasional showers of red cells. Examination of the blood showed 7 Gm. of hemoglobin (Sahli), 2,750,000 erythrocytes, 5,150 leucocytes with 7 juvenile forms, 16 band forms, 62 segmented neutrophils, and 15 lymphocytes. There were about 30,000 platelets per cubic millimeter; the bleeding time was prolonged and the coagulation time was normal. Prothrombin time was eighteen seconds (control sixteen). Culture of the blood on five successive days consistently yielded a luxurious growth of *Streptococcus viridans*, type fecalis.

Roentgenologic examination of the heart revealed slight enlargement in the region of the left ventricle but there was no enlargement in the region of the left auricle. The lung fields were entirely clear and bright. Electrocardiographic studies were normal.

The patient was studied for five days without any specific type of treatment. During this time a short, high-pitched, early diastolic murmur became clearly audible at the apex. Several transfusions of whole blood were then administered and she was started on 50,000 units of penicillin intramuscularly every three hours. This was increased to 100,000 units after forty-eight hours and again to 250,000 units every three hours after another forty-eight hours, because the smaller doses were without effect on her temperature curve, which ranged between 100 and 103.6° Fahrenheit. This was followed by a prompt drop in the temperature to near normal levels for the following ten days. The blood became sterile, but she continued to look unwell. Tachycardia

persisted, she continued to have drenching sweats, and she appeared much weaker than on admission. At this time, it was determined that the organism was completely resistant to penicillin through 5 units per cubic centimeter, but sensitive to streptomycin at 6 units per cubic centimeter. Streptomycin was started intramuscularly in equally divided four-hour doses totalling 1.5 Gm. every twenty-four hours. The temperature rose to 102°F. the following day and the blood culture yielded a scanty growth of the same organism. The drug was then increased to 3.0 Gm. daily and was continued at that level for the following nineteen days. The temperature returned to normal within two days. The blood cultures became consistently sterile and have remained so to date, six months following discontinuance of the drug. Her general condition began to improve and she felt better in every way. On the tenth day of streptomycin therapy she began to notice vertigo on side-to-side movements of the head which gradually increased in severity until she was constantly dizzy by the nineteenth day. This complication became so marked and receded so slowly after streptomycin was discontinued that she was unable to sit in a chair until sixteen days later and even now (six months later) she is unable to walk without assistance. Because of beginning signs of left-sided heart failure, digitalization was carried out on the forty-seventh hospital day, seven days after streptomycin treatment had ceased. Convalescence since that time has been retarded only by vertigo and she is now doing part of her housework each day. Digitalis, however, remains necessary for cardiac compensation.

SUMMARY

A case of subacute bacterial endocarditis due to *Streptococcus viridans*, type fecalis, is presented.

Inasmuch as the patient did not do well clinically on penicillin and because it was impossible to obtain blood levels sufficiently high to inhibit the growth of the organism as indicated by in vitro sensitivity tests, it seems likely that streptomycin was responsible for the eradication of the infection.

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ELECTROCARDIOGRAPHIC ABNORMALITIES IN A CASE OF UREMIA MANIFESTING HYPERPOTASSEMIA

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ALTHOUGH the electrocardiographic manifestations of hyperpotassemia have been studied in detail in animals, only a few such studies have been recorded for man.^{5-7,9,10,12,13} The present case is reported because it provides perhaps an unusually clear demonstration of certain electrocardiographic changes in a uremic syndrome in which hyperpotassemia supervened.

CASE REPORT

W. R. (U. H. No. 771439), a 22-year-old, unmarried, white blocklayer was admitted to the medical service of the University of Minnesota Hospitals on Sept. 20, 1946. He complained chiefly of blurred vision and severe headache.

In 1943, while the patient was a member of the Coast Guard, he experienced an episode of soreness of the throat followed by abdominal pain and red urine. After eight weeks of hospitalization, he was discharged from the Coast Guard. He was then asymptomatic until November, 1944. At that time he is said to have developed pneumonia and to have had microscopic hematuria. Recession of symptoms was again noted until three months prior to admission. At the former time, the patient noted the onset of severe, persistent, occipital headaches which radiated over the entire head. About two months prior to admission, puffiness of the face (about the eyes) and of the legs became manifest. During the three-week period prior to admission, diminishing visual acuity and ocular pain became troublesome. The headaches persisted, but the puffiness had disappeared prior to admission. There was no history of nocturia or of dysuria.

The patient was well developed and well nourished. Oral temperature was 98.2° Fahrenheit. The heart rate was 120 per minute. The respiratory rate was 22 per minute. Examination of the ocular fundi showed bilateral papilledema and numerous areas of hemorrhage and exudate. The examination of the heart showed the point of maximum impulse to be in the sixth left intercostal space at the midclavicular line. The rhythm was regular. Reduplication of the first apical sound and a soft apical systolic murmur were noted. The aortic second sound was of tambour quality. The blood pressure was 170/120. Examination of the lungs and abdomen was negative. Slight costovertebral angle tenderness, bilaterally, was noted. The knee jerks and ankle jerks were hyperactive and equal. The Babinski sign was present bilaterally.

Numerous urinalyses were done. Specific gravities, uncorrected for albumin, ranged from 1.009 to 1.020. Plus 2 albuminuria was recorded on numerous occasions. Granular casts were found on Oct. 4, 1946. Occasional leucocytes and erythrocytes were present in the urine sediments. Urine culture on Sept. 21, 1946, was reported positive for micrococci and diphtheroids. The hemoglobin concentration on Sept. 20, 1946, was 7.0 grams per 100 c.c.; erythrocyte count was 2,100,000. Leucocyte count was 8,700 with 80 per cent neutrophils; 17 per cent lymphocytes; and 1 per cent each of monocytes, eosinophiles, and basophiles. The hemoglobin and erythrocyte

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levels remained essentially the same during the hospital stay. Leucocyte counts of 13,000 and 15,000 were recorded on Oct. 1, and on Oct. 4, 1946, respectively. High neutrophilic percentages (to 96) were present on the latter dates. Sternal marrow biopsy on Sept. 25, 1946, demonstrated "generalized marrow hyperplasia with inflammatory changes, and a relative increase in cells of the erythroid series." Venous pressure was 10 cm. H₂O on Sept. 21, 1946. Total plasma proteins were 4.9 grams per 100 c.c. on Sept. 21, 1946, and serum cholesterol was 354 mg. per 100 c.c. on Sept. 23, 1946. The blood urea nitrogen concentration varied from 86 mg. per 100 c.c. to 236 mg. per 100 c.c. (Chart I). The creatinine range was 13.0 mg. per 100 c.c. to

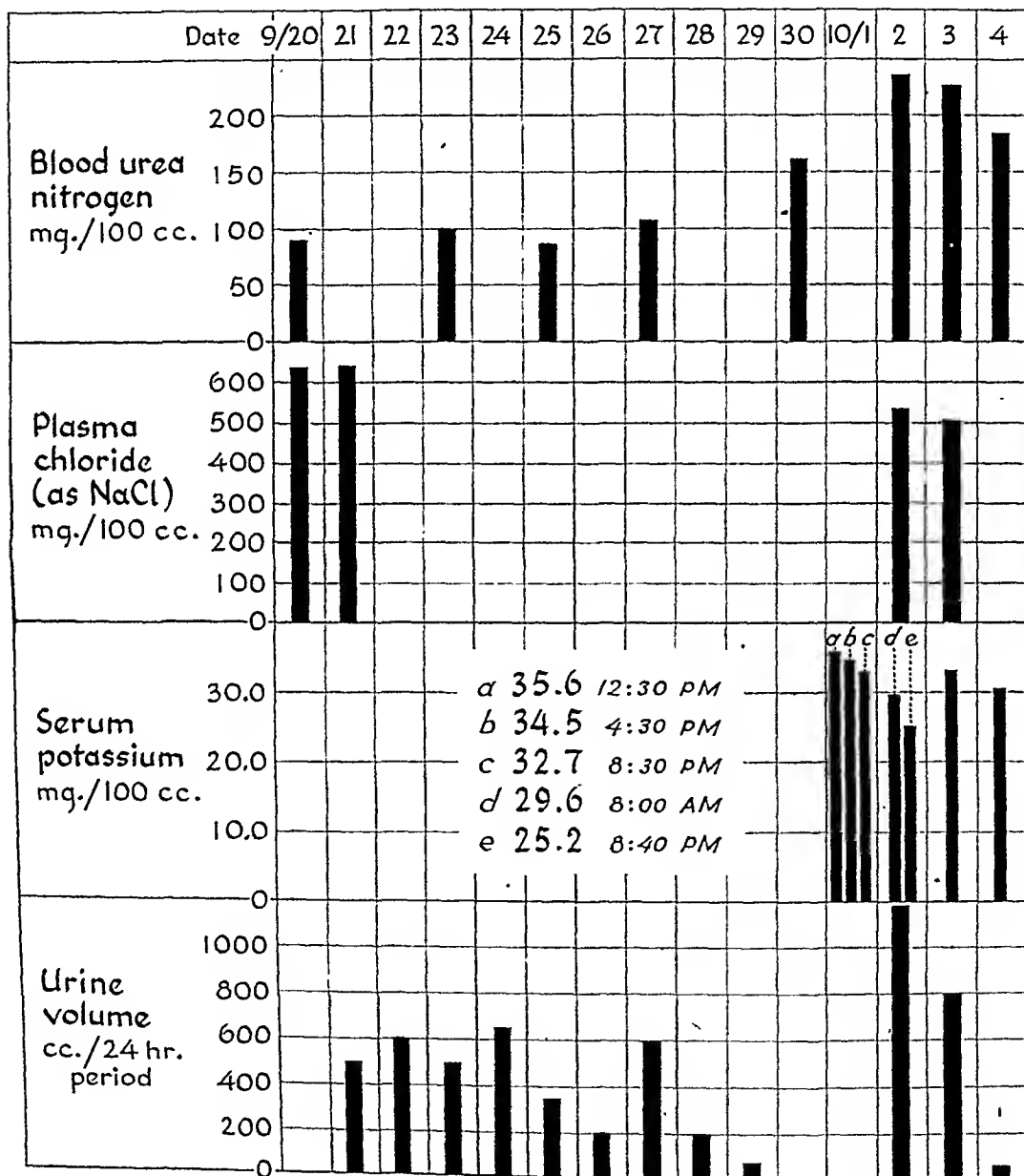


Chart I.

30.5 mg. per 100 c.c. of blood. The uric acid concentration was 5.9 mg. per 100 c.c. of blood on Sept. 23, 1946. The blood glucose concentration was 92.0 mg. per 100 c.c. on Sept. 21, 1946. The range of carbon dioxide combining power of the plasma was 32 to 44 volumes per cent. The serum chloride concentrations (as sodium chloride) were 636 mg. per 100 c.c. and 648 mg. per 100

c.c. on September 20 and 21, respectively; on October 2 and 3, they were 531 mg. per 100 c.c. and 502 mg. per 100 c.c., respectively (Chart I). The serum calcium concentration was 10.1 mg. per 100 c.c. on September 23 and 9.0 mg. per 100 c.c. on October 2. The serum phosphorous was 6.8 mg. per 100 c.c. on September 23 and 21.0 mg. per 100 c.c. on October 2. The range of serum potassium levels was 25.2 mg. per 100 c.c. (6.4 meq. per liter) on October 2 to 35.6 mg. per 100 c.c. (9.1 meq. per liter) on October 1 (Chart I).^{*} Control serum potassium determinations ranged from 15.7 mg. per 100 c.c. to 21.6 mg. per 100 cubic centimeters.[†] An x-ray film made on Sept. 21, 1946, was interpreted as showing left ventricular enlargement.

Patient was afebrile aside from occasional oral temperature readings of 100° Fahrenheit. Blurring of vision and headaches continued throughout the hospital stay. Vomiting, hematemesis, hemoptysis, and epistaxis occurred intermittently. Sudden severe dyspnea and pulmonary edema supervened on Sept. 28, 1946. This episode appeared to respond to intravenous digoxin, morphine, tourniquets, and oxygen. Twenty-four-hour urine outputs are depicted in Chart I. On Oct. 1, 1946, the presence of apparent anuria for the preceding twenty-four to forty-eight hours brought to mind the possibility of hyperpotassemia.⁸ Blood samples for potassium determination were drawn and electrocardiographic studies undertaken. The anuria, supposedly extant on September 30 and October 1, may have been spurious in view of the removal of 1,185 c.c. of urine by catheter on the morning of October 2.

Therapeutic measures consisted of a low protein-low salt diet, barbiturates, paraldehyde, morphine, codeine, atropine, salicylates, penicillin, digitalis, parenteral vitamin B complex, parenteral fluids, and blood transfusion. Pulmonary edema, which followed blood transfusion, prompted the use of 0.25 mg. of digoxin intravenously on September 28. Four cubic centimeters of Digalen (Lilly) were given intramuscularly on September 29 and 30. Two cubic centimeters were given on October 1 and 2. Four cubic centimeters of Digalen were again given on October 4 and 5. No potassium salts were prescribed.

For the most part, the blood pressure readings were 160/100 to 210/150. For about thirty hours prior to death, blood pressure levels within the normal range were found. Repeated examinations revealed no paresis or paralysis. Spasticity, bilateral sustained ankle clonus, markedly hyperactive and equal ankle and knee jerks, and bilateral, abnormal great toe signs were observed on October 1. The patient died at 4:40 A.M. on Oct. 6, 1946. No accurate record of the mode of death is available. Necropsy permission was not obtained. The clinical diagnosis was chronic glomerulonephritis.

Electrocardiographic Findings.—The electrocardiogram of September 21 (Fig. 1) was interpreted as possibly a rather atypical instance of left ventricular strain. The possibility of pericarditis or of recent myocardial infarction was likewise entertained. The electrocardiogram of September 26 (Fig. 1) manifested T-wave changes and slightly increased QRS duration, which together might be regarded (in retrospect) as evidence of potassium effect. The electrocardiogram of September 28 appears to present a stage intermediate between the findings of the two preceding tracings. The electrocardiogram of Oct. 1, 1946 (Fig. 1) was taken in the midst of a period of urinary suppression (Chart I). Intraventricular block, huge peaked T waves, and first degree atrioventricular block have become manifest. A serum potassium determination performed on blood taken simultaneously was 35.6 mg. per 100 cubic centimeters. The tracing made at 8:30 P.M. on October 1 (Fig. 1) demonstrates diminution in severity of intraventricular block, diminution in P-R interval, and receding T-wave changes. The next tracing (Fig. 2), taken on the afternoon of October 2, is characterized by changes of the same general quality as those noted at 12:30 P.M. on October 1 (Fig. 1). The serum potassium level on the morning of Oct. 2, 1946, had decreased considerably, as shown in Chart I. The serum potassium level thirty minutes prior to the electrocardiogram on the evening of October 2 was recorded as 25.2 mg. per 100 cubic centimeters. This tracing shows a marked recession of QRS and T-wave changes, disappearance of

^{*}The method of potassium determination is based on a modification of the methods of Kramer and Tisdall and of Breh and Gaebler, quite similar to the method described by Wood.¹⁹ Our range of normal is 17.7 to 22.2 mg. per 100 c.c. of serum.

[†]One millimole of K=1 meq. of K=39.1 mg. of K.

Uremia, hyperpotassemia

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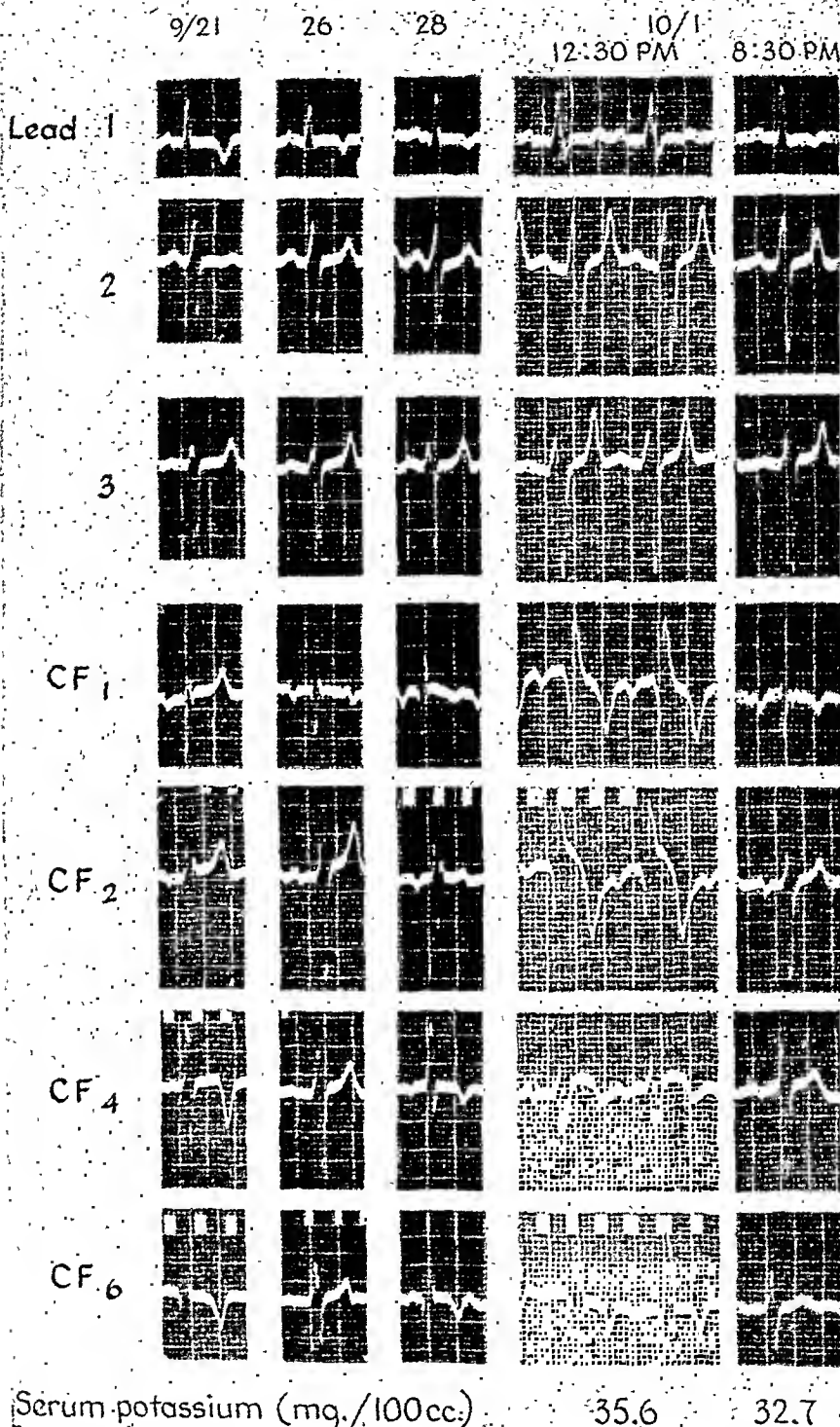


Fig. 1.—Sept. 21, 1946: P-R interval is 0.16 sec.; QRS duration (limb lead), 0.09 sec.; and Q-T interval, 0.37 second. The T waves of Lead I, CF₁, and CF₆ are inverted. The T wave of Lead CF₄ is peaked.

Sept. 26, 1946: QRS, 0.10 second; increased T-wave positivity; T₂ and T₃ peaked. The T wave of Lead CF₂ is tall and peaked. T waves of Leads CF₄ and CF₆ have become upright.

Sept. 28, 1946: Recession of T-wave contours.

Oct. 1, 1946 (12:30 P.M.): Serum K 35.6 mg. per 100 c.c.; P-R, 0.24 sec.; P₂ and P₃ abnormally wide. P₂ barely discernible. QRS 0.14 sec., T₁ upright; T₂ and T₃ are very tall, peaked, and have relatively narrow bases. Q-T is 0.38 second. In Lead CF₁ there is a deep Q; S-T is slightly depressed; and T is inverted and peaked. In Lead CF₂: there is a deep Q; abnormal S-T elevation which blends imperceptibly with a deeply inverted, peaked T wave. In Lead CF₄: S-T segment is +2.5 mm.; inverted T wave. In Lead CF₆: T is inverted, peaked; slight S-T depression.

Oct. 1, 1946 (8:30 P.M.): Serum K 32.7 mg. per 100 c.c.; P waves are normal in duration. Q-T is 0.36 sec.; S-T₁ shows upward bowing. T₁ is inverted. T₂ and T₃ are less prominent. Striking chest lead abnormalities have receded considerably.

Uremia, hyperpotassemia

Univ. Hosp. No. 771439

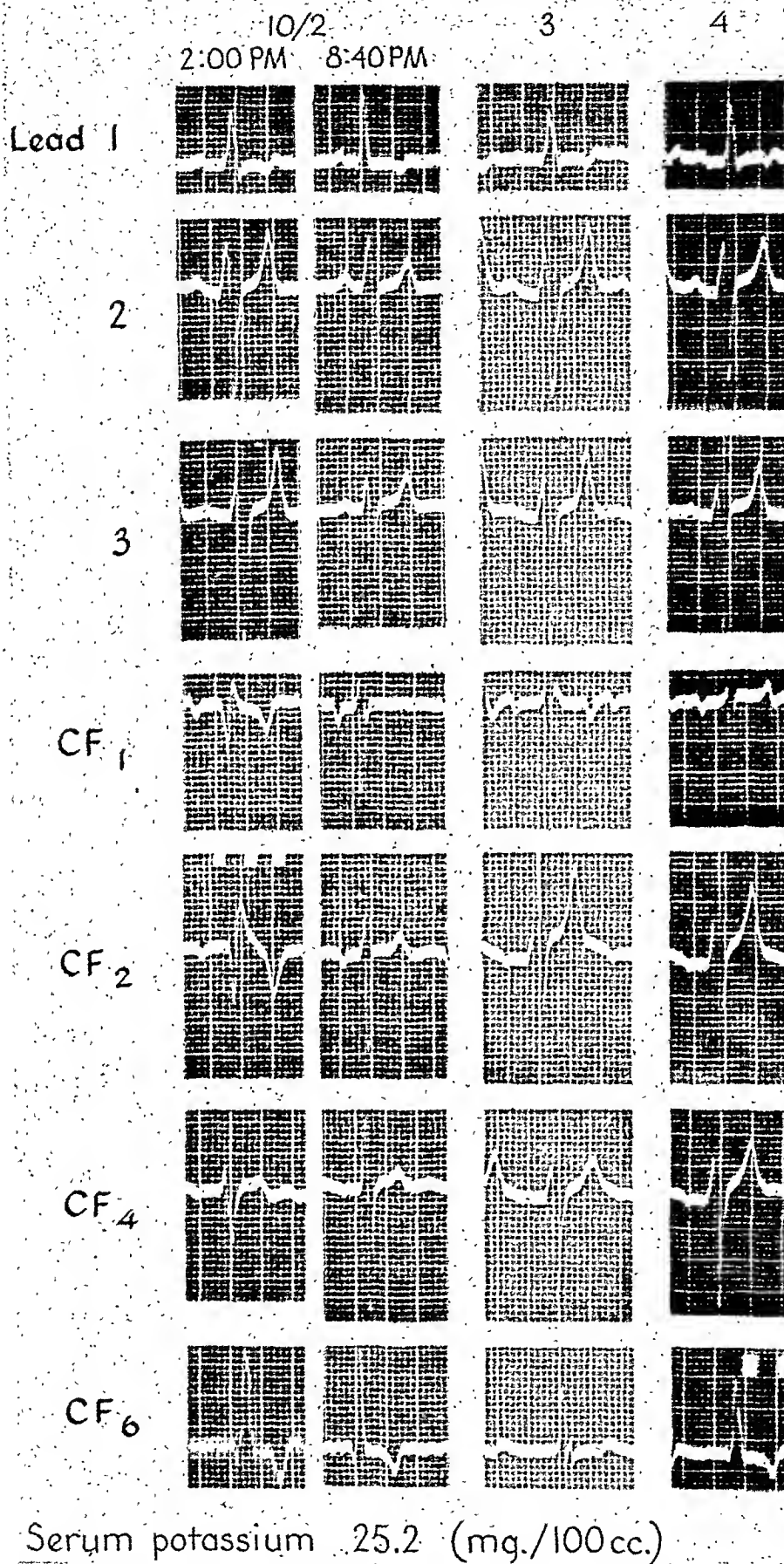


Fig. 2.—Afternoon of Oct. 2, 1946: Reversion to the relatively advanced abnormalities of October 1 (Fig. 1).

Evening of Oct. 2, 1946: Serum K 25.2 mg. per 100 cubic centimeters. Recession of changes apparent in preceding tracing associated with fall in serum K level. Oct. 3, 1946 (10:30 A.M.): Restoration of findings consistent with increasing serum potassium concentration. Oct. 4, 1946: Tracing taken about thirty-six hours before death.

prolonged P-R interval, and a general trend toward the findings of September 28 (Fig. 1). The recurrent conduction disturbances and T-wave abnormalities apparent in the tracing of October 3 (Fig. 2) are probably correlated with a rising serum potassium level (Chart I). On October 4, the serum potassium was 30.8 mg. per 100 cubic centimeters. An electrocardiogram taken on the afternoon of that day (Fig. 2) manifests changes, less pronounced on the whole, than those evident in the preceding tracing.

COMMENT

The salient electrocardiographic abnormalities presented by our patient were: (1) Peaked T waves of large amplitude and relatively brief duration in Leads II and III. These T waves were either inverted or upright in the CF leads; (2) delayed intraventricular conduction; (3) delayed intra-auricular conduction, prolonged P-R interval, and some tendency to disappearance of the P waves (especially in Lead III); (4) the development of a deep Q deflection in CF₂; (5) abnormal S-T elevation, notably in CF₂; (6) variable, changing pattern of abnormalities possibly related to corresponding fluctuations in the degree of hyperpotassemia; and (7) tendency to left ventricular strain.

The first three abnormalities are similar to those ascribed to potassium intoxication in man and in animals. The electrocardiographic concomitants of potassium cardiotoxicity in dogs were first clearly described by Winkler, Hoff, and Smith.^{8,15} Their work appears to have provided the background for and impetus to analogous observations in man. The essential changes were increased T-wave amplitude, S-T depression, defective intraventricular conduction, and P-wave disappearance. No A-V block occurred. Prolongation of the P-R interval was recorded in hyperpotassemic cats studied by Chamberlain and associates,³ and in potassium intoxication in man.^{6,10} The abnormal S-T elevations noted in the present patient do not correspond to the hyperpotassemic S-T depressions observed in dogs and in man. The cause of the deep Q wave in Lead CF₂ is obscure.

Finch and Marchand and their co-workers^{5,6,12} reported six cases of potassium cardiotoxicity. Tall peaked T waves, P-wave absence, S-T depression, decrease in the ratio of R to S, and delayed intraventricular conduction were the chief electrocardiographic findings. In one of their patients⁵ ventricular fibrillation, eventuating in asystole, was recorded terminally. Ventricular fibrillation was not observed in dogs subjected to continuous, slow intravenous infusion of potassium chloride¹⁵ but was observed in an anuric dog to which potassium chloride was administered by duodenal intubation.¹⁷

Keith and associates¹⁰ found P-wave changes (widening and disappearance) and prolongation of the P-R interval in their cases of hyperpotassemia and uremia. Delayed intraventricular conduction and a tendency to peakedness of the T waves were also observed. Katz⁹ recorded electrocardiograms of two uremic patients; in these tracings, peaked T waves were evident in the limb leads and CF leads. No serum potassium levels were mentioned. Govan and Weiseth⁷ recorded limb lead aberrations suggestive of hyperpotassemia in conjunction with a serum potassium of 12.27 mM per liter (48 mg. per 100 c.c.).

The electrocardiographic alterations observed in the present case are comparable to those observed in anuric dogs.⁸ The anuric animals evidenced levels of elevation of serum potassium concentration, sequential electrocardiographic changes, and a mode of death precisely comparable to normal dogs subjected to continuous intravenous potassium infusion.¹⁵ In the latter animals, an increase in amplitude and decrease in duration of the T wave occurred at serum potassium levels of 5 to 8 mM per liter (19.5 to 31.3 mg. per 100 c.c.). Depression of S-T at 8 to 10 mM per liter (31.3 to 39.1 mg. per 100 c.c.), intraventricular conduction delay at 10 mM per liter, P-wave disappearance at 9 to 11 mM per liter (35.2 to 43.0 mg. per 100 c.c.), and cardiac arrest at 14 to 16 mM per liter (54.7 to 62.5 mg. per 100 c.c.) constituted the subsequent electrocardiographic evidence of increasing serum potassium concentration.

Repeated serum potassium determinations in our case disclosed consistently elevated potassium levels. The magnitude of fluctuation of serum potassium appears to be positively correlated with fluctuations in degree of corresponding electrocardiographic change. In this connection, the importance of securing blood for potassium determination at the same time as the electrocardiogram is taken is evident. Further studies of potassium cardiotoxicity in man may determine possible threshold serum potassium levels at which various electrocardiographic abnormalities appear. The critical lethal level in man had been postulated at 10.0 or 10.5 mM per liter of serum.⁶ Survival, despite serum potassium levels of 12.27 mM per liter⁷ and 14.1 mM per liter,¹⁴ has been reported. The fact that other electrocardiographic manifestations in the uremic state (for example, those associated with hypertension, coronary insufficiency, and pericarditis) may result in a somewhat varying electrocardiographic reflection of potassium intoxication from case to case may account for variations to be found in the various case reports.

Persistent anuria or oliguria are presumably the cardinal prerequisites for the development of hyperpotassemia.⁸ Previous case reports^{5,7,10,12} support this hypothesis. The present patient (Chart I) likewise appears to confirm this theory. That potassium intoxication may occur without marked reduction of urine flow is suggested by the following: One of the patients observed by Hoff and associates⁸ was anuric for two or three days preceding death. The serum potassium was 6.5 mM per liter two hours prior to death, and there was no electrocardiographic evidence of potassium intoxication. Some of the reported cases^{5,6,10,12} and the present case manifested hyperpotassemia and related electrocardiographic changes in the absence of complete or nearly complete urinary suppression. Of the factors other than oliguric potassium retention which may be involved in potassium intoxication, the following may be important: (1) a shift of nonplasma potassium into the plasma; (2) renal dysfunction, not directly related to urinary suppression, involving defective conservation and/or excretion of electrolytes; and (3) adrenocortical factors. If the hypochloremia present in our patient (Chart I) indicated concomitant hyponatremia, an influx of potassium from the intracellular fluid may have occurred. This shift of potassium to the extracellular compartment, in association with excess sodium loss

via the kidney and/or defective potassium excretion, may explain the abnormally high serum potassium levels noted in the present case.

Clinically, in association with potassium intoxication, flaccid paraplegia and quadriplegia of sudden onset were observed.^{5,6} These disturbances were not observed in other reported cases^{7,10,12} nor in the present instance. That flaccid paralysis of the family-periodic type may occur in a nonoliguric form of renal insufficiency in a hypopotassemic phase has been suspected.¹ Therapeutic approaches in man and in animals to the problem of potassium intoxication have included the administration of sodium chloride,⁶ insulin,² hypertonic glucose,^{2,7} calcium,^{7,12,16,20} and adrenocortical compounds.^{4,6,18} Whether hypocalcemia and/or hyponatremia occurring in the course of renal insufficiency may enhance the deleterious effects of elevated serum potassium levels is unknown.⁶

In conclusion, it may be well to point out again that the administration of potassium salts to patients in renal insufficiency may be fraught with danger. This practice may be particularly deleterious in the presence of impending or actual urinary suppression. Keith and associates¹¹ observed increases of 6.3 and 10.4 mg. per 100 c.c. in the serum potassium levels following ingestion of 5.0 Gm. of potassium bicarbonate by each of two patients with renal insufficiency. Some of the reported instances of potassium intoxication have involved administration of potassium salts for therapeutic purposes.^{5,7,10} On the other hand, as demonstrated by Winkler and associates,¹⁷ there are many factors which tend to preclude dangerous serum potassium levels following oral administration of potassium salts to patients in states of frank renal insufficiency.

SUMMARY

1. Data are given on a patient who manifested uremia, hyperpotassemia, and electrocardiographic changes consistent with potassium cardiotoxicity.
2. Huge, peaked T waves of relatively brief duration, conduction disturbances, and P-wave changes were the salient abnormalities.
3. A brief discussion of factors which may be involved in the genesis of potassium intoxication was undertaken.

The advice and criticism of Dr. R. V. Ebert are gratefully acknowledged.

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Abstracts and Reviews

Selected Abstracts

Gorham, L. W., Lester, D. E., Wolf, A. V., and Shultz, H. H.: *The Relative Importance of Dietary Sodium Chloride and Water Intake in Cardiac Edema.* Ann. Int. Med. 27:575 (Oct.), 1947.

Thirty patients with edema of congestive heart failure were investigated. Twenty-two of these were maintained on a low salt diet of less than 1.0 Gm. of sodium chloride in twenty-four hours. Eight patients were allowed 3.0 Gm. of sodium chloride in twenty-four hours. The fluid intake was frequently altered. Daily fluid intake varied from 1,000 c.c. to 7,500 c.c. in different patients on different days. When encouraged to do so, most patients took an average of 3,000 c.c. daily. Some were on fluids restricted below 1,500 c.c. throughout the first week of treatment, others were forced to over 4,000 c.c., while still others were restricted during the first three days of treatment and forced during the subsequent four days, and vice versa. These varying intakes were employed during the first seven days because the maximum excretion of sodium occurred during the first week of the regimen. After the first week, fluids were allowed as desired. With a few exceptions, all patients were fully digitalized at least thirty-six hours before the regimen was started. Very satisfactory clinical improvement was noted in the majority of the twenty-two patients treated with less than 1.0 Gm. of sodium chloride in twenty-four hours. Seventeen cases showed a satisfactory clearing of edema. In five cases, maintained four to fifteen days on the less than 1.0 Gm. of sodium chloride in twenty-four hours, there was no apparent clinical improvement. Loss of edema was achieved without recourse to mercurial diuretics. Clinical evidences of edema disappeared usually within one week. No adverse effects were noted which could be directly attributed to the ingestion of extra water. However, five of the patients with chronic edema of long standing responded very poorly to the diet and ingestion of water alone. In these cases, the authors believe that the use of mercurial diuretics was mandatory.

In general, the clinical responses of all the patients seemed to depend on their ability to excrete sodium. Where the sodium chloride excretion was very low, the patients responded poorly. Although forcing fluids caused some increase in sodium and water loss, the slightly negative sodium balance was seemingly not enough to affect the clinical course. However, in none was there any adverse effect from the ingestion of copious amounts of water when the diet was kept low in sodium.

This regimen is not considered by the authors to be a substitute for mercurial diuretics, especially in the more refractory cases. The relative sodium loss of three to five days on the regimen for the average patient was only the equivalent of that obtained by 1.0 c.c. of Salyrgan. Nevertheless, they consider that the low sodium diet and moderate intake of water (3,000 c.c. daily) appear to be most valuable adjuncts to digitalis and the mercurial diuretics in the treatment of cardiac failure.

WENDKOS.

Reader, G. G., Romeo, B. J., Webster, B., and McDermott, W.: *The Prognosis of Syphilitic Aortic Insufficiency.* Ann. Int. Med. 27:584 (Oct.), 1947.

In 1942, the authors had under their direct observation ninety-one patients suffering from syphilitic aortic insufficiency. In forty-seven of this number, supplementary studies, such as

circulation time, venous pressure, vital capacity, and teleroentgenogram of the chest, were made. Thirty of this carefully studied group of patients are known to be still alive, but only twenty-seven of the original group of forty-seven were available for comparative study and symptomatic appraisal. Of this number, sixteen have remained asymptomatic; three admitted to mild symptoms of cardiac failure on careful questioning, and eight presented frank evidences of myocardial insufficiency such as exertional and/or paroxysmal nocturnal dyspnea. Of the sixteen who are asymptomatic, ten are 60 years of age or older, while the remaining six range in age from 43 to 59 years. Most of these asymptomatic patients are still working. Of the eight who complained of dyspnea, two are 60 and 71 years of age, respectively, whereas the remainder range in age from 35 to 57 years. In the symptomatic and asymptomatic groups, aortic insufficiency has been known to be present for approximately the same length of time, that is, for five to twelve years, with an average of 7.6 years. Compensation has been restored by treatment with digitalis in nine of the symptomatic group. The symptomatic phase in this group has varied from two to fourteen years, with an average of 5.6 years. Nine of the total number of surviving patients had been in congestive heart failure three to nine years previously and had responded very well to digitalis. All the patients included in this study had received continuous antisyphilitic therapy with bismuth and arsenicals for approximately four years.

Abnormal widening of the aorta did not appear to be a factor affecting the prognosis, whereas a low diastolic blood pressure was recorded in only two of those who have survived the five year follow-up period. The intensity of the murmur did not seem to bear any relationship to the ultimate outcome, since a loud diastolic murmur was frequently heard in those who had remained asymptomatic while the murmur was soft in many who had always been symptomatic. It is the conclusion of the authors that of all the tests available, the circulation time and the diastolic blood pressure probably offer the best index of prognosis in syphilitic aortic insufficiency.

WENDKOS.

Melvin, J. P., Jr.: Post-partal Heart Disease. Ann. Int. Med. 27:596 (Oct.), 1947.

Four female Negro patients, two of whom were 21 years of age and the other two 31 and 32 years of age, developed congestive heart failure during the postpartum interval, shortly after the uncomplicated delivery of their respective infants. There was no history of antecedent rheumatic infection nor syphilis in the entire group and serologic tests were uniformly negative. In all cases, the diet appeared to be adequate throughout pregnancy and there were no stigmata of nutritional deficiency which could be detected in the physical examination. Temporary elevations of the diastolic blood pressure were noted in all cases during the phase of cardiac decompensation. Ectopic rhythms were not present. The only adventitious cardiac sounds consisted of transient systolic murmurs and protodiastolic gallop rhythms. Teleroentgenograms of the chest in all instances revealed definite cardiac enlargement, which disappeared following restoration of cardiac compensation. Low-grade fever was present in one case but the cause for the pyrexia was never established in spite of repeated blood cultures. In all four instances, uneventful recovery from the congestive heart failure followed bed rest, diuresis, and digitalis, whereas no benefit seemed to result from the administration of concentrates of vitamin B complex. The author considers that the clinical findings in these cases confirm previous concepts that reversible disease of the heart, directly incidental to pregnancy, may be a definite clinical entity.

WENDKOS.

Underdahl, L. O., and Smith, L. L.: Coronary Artery Disease in Women Under the Age of Forty. Proc. Staff Meet., Mayo Clin. 22:479 (Oct. 15), 1947.

The authors studied the records of 95,000 women under the age of 40 years who were seen during the eleven-year period, 1935 through 1945, and found a total of twenty-seven patients in whom there was no reasonable doubt of the diagnosis of coronary disease. The ratio is, therefore, one case of coronary artery disease in every 3,500 patients. This series included cases of coronary sclerosis with angina pectoris and coronary sclerosis with myocardial infarction. The criteria for diagnosis are the same for coronary disease in women under the age of 40 years as in any other group. In this series, there was only one patient who had diabetes.

There were seven patients who had definite myocardial infarction and two others who had questionable infarction. Of these seven patients, two died suddenly while under observation in the hospital and another died five weeks after returning home. The remaining twenty patients had coronary sclerosis with angina pectoris. Two of these had a history which suggested previous myocardial infarctions, but the diagnosis could not be proved.

Of the twenty-seven patients, only one was under the age of 35 years. Thirteen of the twenty-seven patients had varying degrees of obesity. Seventeen of the patients (63 per cent) had varying degrees of hypertension. Of the five patients who were of normal weight and had infarction, four had hypertension; the fifth had neither obesity, hypertension, nor hyperlipemia. Of fourteen patients who had blood fat determinations, eight showed elevation and six had normal values.

The results of this study confirm previous impressions that coronary disease in women under the age of 40 years is very rare.

BELLET.

Lewis, L. A., and Page I. H.: Changes in the Plasma Protein Pattern (Tiselius Electrophoretic Technique) of Patients With Hypertension and Dogs With Experimental Renal Hypertension. J. Exper. Med. 86:185 (Aug.), 1947.

Employing the Tiselius electrophoretic technique, the author studied the plasma protein pattern of ten patients with essential hypertension, sixteen patients with malignant hypertension, that of six dogs before and after the development of hypertension induced by wrapping both kidneys in silk, and that of three dogs in which the spleen was wrapped in silk. The sixteen patients with malignant hypertension were classified according to the severity of the disease into mild, moderate, and severe cases. The proteins studied were albumin, alpha, beta, and gamma globulin, and fibrinogen.

The plasma protein pattern of the patients with uncomplicated essential hypertension showed only slight variations from the normal. In those with severe malignant hypertension, the fibrinogen and beta globulin were usually elevated and the albumin increased. These changes were less marked in less severe cases of malignant hypertension. In the dogs with experimental hypertension, the gamma globulin level was greatly elevated, and in one dog with the malignant hypertension syndrome, beta globulin and fibrinogen were also increased. It is concluded that elevation of beta globulin seems in some manner to be associated with the occurrence of severe vascular disease.

MERANZE.

Miale, J. B.: Characteristic Urinary Findings in Visceral Angiitis. (Periarteritis Nodosa, Lupus Erythematosus). Am. J. Clin. Path. 17:820 (Oct.), 1947.

Urinary findings in three cases of visceral angiitis (periarteritis nodosa, lupus erythematosus) are listed. These consist of erythrocytes and erythrocytic casts, waxy casts, fatty casts, broad casts, and "oval fat bodies." This urinary picture has been described so seldom in acute glomerulonephritis that it is considered presumptive evidence of the presence of visceral angiitis in the acute phases. These findings disappear with remission of the disease.

MERANZE.

Jones, J. C.: Complications of the Surgery of Patent Ductus Arteriosus. J. Thoracic Surg. 16:305 (Aug.), 1947.

Jones discusses the types of morbidity and mortality incident to the operative management of sixty-one consecutive patients with patent ductus arteriosus. In none of the patients was there a preoperative bacterial endarteritis. In fifty-three patients the ductus was ligated and in eight it was completely divided and sutured. Two deaths occurred. One occurred during operation when a massive hemorrhage from the ductus necessitated division and suture; cardiac arrest developed and resuscitation was unsuccessful. The second death occurred forty-eight days

following ligation; autopsy showed a re-established fistula around the ductal ligatures between the pulmonary artery and the aorta. In addition, an aneurysm of the ductus was found. During the two weeks before death a blood stream infection with *Staphylococcus aureus* associated with a high fever developed. Vegetations were found on the walls of the pulmonary artery and aorta.

Of the fifty-nine living patients, ten have clinical evidence of either recurrence of the fistula or inadequate obliteration of the ductus. All but one of this group, however, are well.

Two patients developed aortobronchial fistulas with intermittent hemoptysis, necessitating operative intervention in one of them. The two umbilical tapes had eroded into the aorta and a small bronchus of the left upper lobe. The opening into the aorta was sutured and a complete recovery ensued. Other complications included atelectasis, pneumonia, and two cases of empyema.

LORD.

Gross, R. E.: Complete Division for the Patent Ductus Arteriosus. J. Thoracic Surg. 16:314 (Aug.), 1947.

Gross supports his contention that the patent ductus should be divided and sutured in every case subjected to operation by the facts that there have been only four deaths in 180 consecutive cases, whereas in forty-three patients treated by some form of ligation, there were three deaths and a recurrence or continuation of the fistula in approximately eight cases. Since complete division in the author's hands carried a mortality no higher, but rather lower, than ligation of the ductus, and since complete division cannot be followed by recurrence, he has employed it routinely in all cases, infected as well as uninfected, for the past three years.

The technique is illustrated and described in detail. An anterior approach through the left chest with reflection of the breast cephalad is employed. Careful and complete dissection of the areolar and fibrous tissue from the ductus and adjacent pulmonary artery and aorta is essential. The ductus is divided between four clamps and after removal of the two innermost clamps, each end is sutured with 00000 Deknatel silk. There has been no instance of immediate or delayed hemorrhage or aneurysm.

LORD.

Conant, J. S., and Kurland, L. T.: Pulmonary Tuberculosis Associated With Anomalous Common Left Pulmonary Vein Entering the Left Innominate Vein. J. Thoracic Surg. 16:422 (Aug.), 1947.

The authors report the occurrence of an anomaly of the left common pulmonary vein in a 37-year-old Negro. Bilateral pulmonary tuberculosis was discovered four years before his death in 1946. The lesions in the right lung responded well to rest and other measures, but a cavity in the left upper lobe enlarged progressively from 3 cm. to 10 cm. in diameter during the four-year observation period. Death followed rapidly the development of a right pleural effusion.

Necropsy showed that the left auricle received only one pulmonary vein, that from the right side, which divided as it passed through the pericardium. The circulation of the right lung was normal. Further exploration of the pulmonary circulation showed a common left pulmonary vein emptying into the left innominate and picking up a tributary from what appeared to be the left hemiazygous above the level of the left pulmonary artery.

It would appear that by itself recirculation of aerated blood from one lung into another, by a shunt involving half the pulmonary bed, still provides an adequate pulmonary reserve. In the case reported, the arterial blood received all its oxygen from the right lung. The addition of pulmonary disease to the picture suggests in this instance that the integrity of the right lung was more important than that of the left. Obstruction to the flow of blood through the right lung, which was directly concerned with maintaining the oxygenation of the systemic circuit, had a more serious effect than involvement of the left lung. Up to the time the patient suffered his terminal episode, the tuberculosis was more extensive on the left side. When spread to the right lung occurred and was associated with a right-sided effusion, the supply of oxygen and blood to the systemic circuit then became limited.

LORD.

Corcoran, D. B., and Coleman, F. P.: Anomaly of Aorta Simulating Mediastinal Tumor. *J. Thoracic Surg.* 16:427 (Aug.), 1947.

Corcoran and Coleman point out that many mediastinal tumors are asymptomatic and are discovered only during routine roentgenologic examination. Following discovery of such a lesion, an accurate differential diagnosis may be difficult, although Coleman was able to determine the cellular nature of the pathology preoperatively in eleven of nineteen cases.

Aneurysms and anomalies of the thoracic aorta are sometimes mistaken for mediastinal tumors and the authors report such a case. A 58-year-old man was found by roentgenographic examination of the chest to have a dense mass in the posterior mediastinum between the levels of the seventh and tenth ribs. It bulged laterally into the left hemithorax and displaced the barium-filled esophagus anteriorly. At operation a markedly elongated descending thoracic aorta was found which had a horseshoe-shaped curve. The authors discuss the possible embryologic origins of such an anomaly.

LORD.

Jampolis, R. W., Jenkins, H. P., Newman, M. M., and Nardi, G. L.: Control of Hemorrhage From the Cardiac Auricles by the Gelatin Sponge, An Experimental Study. *Surgery* 22:198 (Aug.), 1947.

In Elkin's series, in 1944, the mortality rate in wounds of the four cardiac chambers, the aorta, and the pulmonary artery was 22 per cent. In three cases of injuries to the auricles, there was one death, a mortality rate of 33 per cent. In a series of forty-two patients with wounds of the heart reported by Griswold and Maguire, the wounds in four were in the auricles, and three of these patients died. The present authors point out that there are a number of factors which are responsible for the high mortality rate in wounds of the auricles. First, the left auricle is difficult to expose; second, the walls are thin and friable, making the hemorrhage large and rapid, as a rule, and making suturing difficult.

In a group of eighteen dogs, the tip of the auricular appendage was removed and a knife was thrust into the auricular wall at the base of the appendage in order to produce severe hemorrhage. A gelatin sponge was applied to the defect and held in place for ten minutes. It is compressed, used dry, and Cilkloid is employed to prevent the sponge from adhering to the surgeon's glove. There were no instances of secondary hemorrhage. At autopsy the sponge was adherent to the epicardium and was absorbed in from five to eight weeks. The authors present their experiments as a technique which might have "value in clinical surgery as an aid in controlling hemorrhage in stab wounds or bullet wounds of the auricles, in injury of the auricle in the course of pericardiectomy, and in operative procedures on cardiac valves."

LORD.

McSwain, B., and Spencer, F. C.: Carotid Body Tumor in Association With Carotid Sinus Syndrome. *Surgery* 22:222 (Aug.), 1947.

Although 275 cases of carotid body tumors have been reported in the literature, only six unequivocal cases of the carotid sinus syndrome have been recorded in association with carotid body tumors. The authors add two new cases. In one patient, a boy, 15 years of age, there was a 2-year history of fainting spells and a mass in the neck of one year's duration. Pressure on the mass, which was located in the left side of the neck just below and posterior to the angle of the mandible, caused cardiac slowing, an imperceptible blood pressure, and syncope. Following release of pressure, the blood pressure and pulse rate returned to normal in one minute. At operation it was necessary to resect portions of the common, internal, and external carotid arteries in order to extirpate the tumor. On microscopic study it was found to have invaded the coats of the common carotid artery. The cellular elements were typical of a benign adenoma or tumor of the carotid body. The patient made an uneventful recovery and has remained free from further syncopal attacks. Two and one-half years after operation, a 2.0 x 2.0 x 1.0 cm. mass was found in the region of the bifurcation of the right common carotid artery. No symptoms were caused by pressure upon the mass. Excision of the tumor has been advised.

The second case was a 28 year-old woman who had had many attacks of syncope associated with turning of the head over a period of eight years. A mass in the left side of her neck had been present for three years. Syncopal attacks ceased three years before admission and were replaced by sensations of faintness. For one month, the patient had noted atrophy of the left side of the tongue. At operation the common, external, and internal carotid arteries were ligated and the mass removed. The internal carotid artery was found to be thrombosed. Microscopically, the specimen was typical of a carotid body adenoma. Postoperatively, a transient right-sided hemiplegia occurred but disappeared completely in forty-eight hours.

In both operations it was necessary to sacrifice several nerves, resulting in left vocal cord paralysis in both patients and a Horner's syndrome in the first case.

The authors discuss the possible theories of the spontaneous disappearance of the carotid sinus syndrome in the second case of carotid body tumor and suggest that thrombosis of the internal carotid artery may have abolished the cerebral type of reflex. They favor, however, the concept that the tumor may have destroyed the afferent nerve connection from the carotid sinus, thereby breaking the reflex arc.

LORD.

Simeone, F. A., and Sarnoff, S. J.: The Effect of Dibenamine on the Autonomic Stimulation. Surgery 22:391 (Aug.), 1947.

An experimental study was performed on cats to determine whether Dibenamine blocks the effects of sympathetic nerve excitation, as well as the action of epinephrine. The nictitating membrane, disconnected from the central nervous system by severing the cervical sympathetic trunk, was utilized as a test organ. The membrane was previously sensitized by postganglionic denervation.

The data demonstrated that Dibenamine blocks the positive action of epinephrine, at the same time unmasking its negative effects. The action of sympathin E is also blocked. However, the blocking effect is not as great in the case of the changes produced by sympathetic nerve stimulation. Dibenamine does not inhibit at all the cardioacceleration following excitation of the cardiac nerve and only diminishes, but does not abolish, the contraction of the nictitating membrane in response to stimulation of the cervical sympathetic nerves.

Since the effect of Dibenamine is not immediate, the authors suggested that the action of the drug is not a direct one upon epinephrine or sympathin, but rather that it effects some substance between the mediator and the contractile mechanism or possibly the contractile mechanism itself. The latter theory appears to fit the facts best.

ABRAMSON.

Loewe, L.: Anticoagulation Therapy With Heparin/Pitkin Menstruum in Thromboembolic Disease. Am. J. Med. 3:447 (Oct.), 1947.

This is one of a series of seminars on thromboembolism. The author's experience with the use of heparin/Pitkin menstruum in a series of more than 400 patients receiving several thousand subcutaneous deposits is the basis of the report. The functional pathology of intravascular clotting is reviewed and the disadvantages and limitations of surgical interruption of veins and the use of Dicumarol in thrombophlebitis and/or phlebothrombosis is discussed.

The author feels that heparin is uniquely applicable in thromboembolic disease and that the heparin/Pitkin menstruum circumvents previous disadvantages of the substance. Composition, dosage plan, method of administration, clinical use, and method of following the patient's clinical course are discussed in detail.

Local pain, swelling, and tenderness caused by the earlier preparations do not occur with the present preparations. Suspension of heparin activity may be obtained with small transfusions of whole blood. It is felt that the substance is safe, simple, practical, and effective for anticoagulation therapy.

An analysis of the clinical results in 251 patients representing all forms of venous thromboembolic disease revealed good results. There were five fatalities. Loewe believes that there is a parallelism between thrombus mass and heparin requirements. In uncomplicated phlebothrom-

bosis, heparinization need be continued only for seven to ten days, while cases complicated by pulmonary infarction require an additional seven to ten days of heparinization. The liberal use of papaverine is recommended.

The problem of prophylaxis in the field of thromboembolism, as it pertains to heparin/Pitkin menstruum, is discussed, as well as the treatment of arterial thromboembolic disease (peripheral vascular disease, cerebral thrombosis, and coronary artery thrombosis).

WOODS.

Boger, W. P., Kay, C. F., Eisman, S. H., and Yeoman, E. E.: Caronamide, a Compound That Inhibits Penicillin Excretion by the Renal Tubules, Applied to the Treatment of Subacute Bacterial Endocarditis. Am. J. M. Sc. 214:493 (Nov.), 1947.

It is now established that approximately 80 per cent of the loss of penicillin from the body is by way of the renal tubules. Therefore, an agent capable of inhibiting tubular excretion might be expected to enhance the levels of penicillin in the plasma. These effects have been observed to follow the administration of Diodrast, para-aminohippuric acid, and benzoic acid. Diodrast and para-aminohippuric acid have been employed in the treatment of subacute bacterial endocarditis, but the necessity of administering large amounts of either substance by constant intravenous infusion has limited their usefulness.

A new compound, Caronamide, has been described as being effective in elevating the plasma concentrations of penicillin. It has been hypothesized that the physiologic and reversible inhibition of the penicillin transport mechanism under these circumstances is due to a substrate competition between penicillin which is excreted by the tubules, and Caronamide (4'-carboxy-phenyl-methane-sulfonanilide) which is essentially refractory to excretion by the transport mechanism. In preliminary clinical investigations, penicillin plasma concentrations were enhanced from three to seven fold by the oral administration of Caronamide, and no serious toxic manifestations were observed. Accordingly, the treatment of a case of subacute bacterial endocarditis due to a strain of *Streptococcus viridans* resistant to penicillin and streptomycin was considered to be justified.

The patient was a 51-year-old woman who had suffered relapse following each of two courses of penicillin therapy. The sensitivity of the organism to penicillin had originally been 0.03 unit per cubic centimeter, but after the second course it was 0.5 unit per cubic centimeter. Two courses of streptomycin were then administered, but cure was not effected and there was a 20,000-fold increase in the resistance of the organism to this antibiotic. Following the failures with streptomycin, penicillin was again administered, but this time in association with oral Caronamide in dosage ranging from 12 to 24 Gm. per day. It was possible by this combination to elevate the plasma concentration to the remarkable height of from 30 to 60 units of penicillin per cubic centimeter. On the ninth day of this course, the blood cultures became negative and remained so thereafter. Another combined course was given later for prophylactic purposes when the patient had a tooth extracted. No reactivation of the disease occurred. It was estimated that the blood levels which were obtained in this case with combined treatment could only have been obtained with penicillin alone had 10,000,000 units daily been administered.

DURANT.

Minkowski, W. L.: The Coronary Arteries of Infants. Am. J. M. Sc. 214:623 (Dec.), 1947.

Considering the enormous volume of literature devoted to the coronary arteries, the dearth of attention given these vessels in the newborn, infants, and children is rather surprising. A few investigators have included the coronary arteries of young people in overall surveys of age changes occurring in these vessels; none have studied infantile coronary arteries in numbers adequate for statistical analysis. To meet this need, there are reported the histologic studies on the coronary arteries of 204 infants, most of whom died at birth or soon afterward. The causes of death were, in general, limited to birth injuries and/or asphyxia, inflammatory processes, and a small number of miscellaneous diseases unrelated to either of the former groups. Sections about 5.0 mm. thick were taken from each of the three major coronary arteries at a distance of 0.5 to 1.0 cm. from their origins. A special magnification technique was used for the measurement of the areas of the intima and media.

It was found that 60 per cent of 122 male subjects and 51 per cent of eighty-two female subjects revealed a musculoelastic and/or an elastic hyperplastic layer in one or more of their coronary arteries. It may, therefore, be concluded that coronary intimal thickening occurs in a large number of newborn infants and children dying of various causes. In a group of fifty-one boys and twenty-five girls less than one day old who died of birth trauma and/or asphyxia, the mean difference between the male and female intima-media rates of 2.6 times the probable error of the means was obtained. This is considered to be a highly suggestive difference. The validity of this difference and of that in Dock's material must be determined by examination of greater numbers of hearts.

The role played by infection was also of great interest in this study. Bronchopneumonia was a very common infection in the series of cases studied. For the entire group, and particularly for the group more than one month old, the differences in means for coronary intimal thickening between the group with infection and the group without infection were clearly significant.

The meaning of the intimal thickenings found in this study, particularly as it concerns the subsequent development of coronary arteriosclerosis, remains to be clarified.

DURANT.

Barany, F.: Peripheral Blood-Flow in Rabbits With Experimental Hypertension.

Acta med. Scandinav. 127:376 (No. V), 1947.

The author repeated the experiments of Kapp, Friedland, and Landis (1941) which had shown that the ear temperature of rabbits with nephrogenic hypertension remained the same when the animals were warmed to 40° centigrade. It had been inferred that an increase in vascular resistance occurred in the skin directly proportional to the blood pressure increase. Because he felt the rabbit's ear was primarily a heat radiator and therefore its temperature a poor index of cutaneous blood flow, the author repeated the experiments, measuring not only the temperature of the ear, but also that of the forepaw in warmed rabbits with hypertension produced by the Page cellophane technique.

There was no evidence of vasoconstriction associated with the increased pressure, as compared with controls, when the forepaw was used. The ear temperature remained constant just as it did in the 1941 experiments.

Since patients with renal hypertension do not have an increase in skin blood flow and, therefore, are assumed to have vasoconstriction in the cutaneous bed, there appears to the author to be an important difference between human and rabbit renal hypertension; there is either a different etiological agent or a different response to the same agent.

SAYEN.

Oster, J.: Arterial Hypertension in a Child, Cured by Nephrectomy. *Acta med. Scandinav.* 128:42 (No. I), 1947.

After reviewing the unilateral renal affections associated with hypertension, the author reports the case of a 7-year-old boy with intermittent leftsided hydronephrosis ascribed to pressure of an aberrant artery on the ureter. The blood pressure was not determined preoperatively. A darning-needle-sized aberrant artery to the lower of the kidney pole was found and ligated. After one month, headache, nausea, and vomiting appeared from time to time, and five months after operation, the child developed hypertensive encephalopathy with a blood pressure of 200/170. After the acute encephalopathic bout subsided, the blood pressure was 180/130 and the blood urea nitrogen 36 mg. per cent.

Left nephrectomy was performed and pathologic examination of the kidney revealed changes in the lower pole thought to be due to ischemia, in addition to slight hydronephrosis throughout the organ. The blood pressure fell to normal and fourteen months later was 90/60, the child remaining well. Although there was not entirely convincing proof in this case of a causal relation between ligation of an aberrant renal vessel and hypertension (the duration of the hypertension being uncertain), the author points out the possible danger of such ligations, which, he believes, is not sufficiently realized.

SAYEN.

Peters, J. T.: The Necessity and Possibility of Giving Detoxified Large Oral Doses of Salicylates in the Treatment of Rheumatic Fever in Order to Prevent or Cure the Inflammatory Stage of Carditis. *Acta med. Scandinav.* 128:51 (No. I), 1947.

On the basis of "numerous" cases treated since 1929, it is asserted that the dosage of salicylate used in active rheumatic fever is usually insufficient, and that remarkable results can be obtained if blood levels of 35 to 70 mg. per cent are reached. This cannot be accomplished safely with intravenous administration or the usual methods of oral administration. However, if sodium bicarbonate be given in solution in a ratio of 2.0 Gm. for every gram of sodium salicylate, it is possible to give 15 Gm. of salicylate orally each twenty-four hours with relative impunity. The author's formula consists of sodium salicylate, 30 Gm.; sodium bicarbonate, 60 Gm.; and peppermint water, 300 c.c., made up to 1 liter with cold distilled water. Fifty cubic centimeters of this solution are given ten times a day, the dosage being proportionately reduced for children. The importance of administering the salicylate in solution and in not heating the solution while preparing it (to prevent formation of sodium carbonate) is stressed. Neither alkalosis, nor respiratory stimulation, nor vomiting was seen when salicylate was administered in this form and in this dosage. Continuance of therapy till all evidences of activity subsided was important. The sedimentation rate became normal rather early and was not the best guide. A marked decrease in the frequency and severity of carditis is claimed.

SAYEN.

Adler, E., and Lyon, E.: Cardiac Disorders Associated With Infectious Hepatitis. *Cardiologia* 11:111, Fasc. 3, 1947.

Seven per cent of a large number of cases of infectious hepatitis with icterus had cardiovascular symptoms and signs. Eight cases are reported and their electrocardiograms shown. The symptoms occurred during the infection, immediately after the acute phase, and after variable intervals following the infection. The subjective complaints were palpitation, dyspnea, pressure sensation in the chest, anginoid pain with occasional radiation into the left arm, fatigue, weakness, and occasional arrhythmias. The ages varied from 20 to 40 years and all were previously healthy. Marked variations in heart size or abnormal auscultatory phenomena were absent.

All cases showed electrocardiographic changes considered to be characteristic of myocarditis. In some cases a return to normal was observed. Changes in A-V conduction, in the form and displacement of the S-T segment at rest and after exercise, and flattening or inversion of the T waves were observed. In addition, sinus arrhythmias and auricular or ventricular premature contractions were noted. In almost all cases the duration of the Q-T segment was prolonged. This is considered to be toxic in origin. In several cases, excessively high T waves were found.

LENEL.

Hedinger, C.: Contusion of the Heart With Late Rupture of the Left Ventricle. *Cardiologia* 12: Fasc. 1/2, 1947.

A 53-year-old soldier was kicked in the chest by a horse. Following this episode, he was hospitalized for three days because of severe dyspnea. After discharge he was unable to perform his usual duties and three days later he was again hospitalized. A pericardial friction rub was heard over the precordium. The pulse rate was 120; blood pressure, 120/100; and white blood cell count, 19,200, with 82 per cent polymorphonuclear leucocytes. Fluoroscopy showed enlargement of the heart and pulmonary congestion. The patient died suddenly on the ninth day after the accident.

Autopsy showed a fracture of the sternum at the level of the fourth rib and fracture of the cartilages of two ribs. Examination of the heart revealed a tear of the lateral leaflet of the tricuspid valve; rupture of the descending branch of the left coronary artery near its origin from the aorta, with formation of a dissecting aneurysm and a recent thrombosis of this artery; a very large recent infarct of the left ventricle with mural thrombosis and pericarditis; and rupture of the left ventricle in the region of the infarct with hemopericardium.

The author advocates a longer period of observation after severe trauma to the chest.

LENEL.

Mahaim, I.: New Concepts Concerning the Treatment of Mitral Stenosis. *Cardiologia* 12: Fasc. 1/2, 1947.

Mitral stenosis is not always due to scarring of the mitral valve but may be caused by a myxomatous polyp originating in the left atrium and protruding through the mitral orifice. Such polyps may cause arterial myxomatous emboli which can be identified as such after surgical removal. Such polyps are a constant threat to the life of the patient.

The diagnosis can be made by the following suggestive signs and symptoms: The sudden appearance of mitral stenosis in a subject with a negative cardiac history and the sudden appearance of peripheral signs of marked decrease in cardiac output and peripheral embolism. Angiocardiography may reveal the left atrium to have a lacunar appearance.

The author suggests that mitral stenosis due to a polyp and also mitral stenosis due to scarring should be treated surgically by the production of an artificial interauricular septal defect. This recommendation is supported by the fact that patients with mitral stenosis and an associated interauricular septal defect show no evidence of pulmonary congestion, and survive longer than patients with mitral stenosis alone.

LENEL.

De la Barreda, P., Diaz, C. J., and de Molina, A. F.: Neurochemical Regulation of Arterial Pressure (the Endocrine Function of Arteries). *Rev. españ de cardiol.* 1:1 (Jan.), 1947.

Stimulation of the central stump of the vagus nerve in dogs produces a temporary hypertensive effect even after removal of the pituitary gland or the adrenals, and after extirpation of liver or kidneys. The effect is blocked by section of the medulla. It is assumed that the effect is mediated to the vascular tree via the spinal cord and the peripheral nerves. The hypertensive response may be obtained in crossed circulation experiments in the nonstimulated animal. It may be observed in a dog that has been transfused with plasma obtained during or shortly after the stimulation of the vagal stump. Plasma from such animals greatly reduces flow of fluids in a Loewen-Trendelenburg preparation of the frog. The hypothetical hypertensive substance is not inhibited by ergotamine. The phenomenon may represent an example of internal secretion of the arterial walls or of certain endothelial structures (glomus bodies), perhaps similar to the assumed production of renin by the juxta glomerular apparatus.

HECHT.

Manning, G. W., and Caudwell, G. C.: The Effect of Demerol, Ergotamine, and Dihydro-Ergotamine on Mortality After Coronary Occlusion in Dogs. *Brit. Heart J.* 9:85 (April), 1947.

The authors report the result of Demerol and sympathetic inhibiting agents upon acute coronary occlusion in conscious dogs, using the same experimental conditions and procedures previously described (Manning and associates, 1939). The sympathetic inhibiting drugs used were ergotamine tartrate (Gynergen II, Sandoz) and a new ergot derivative, dihydro-ergotamine (DHE₄₅, Sandoz).

Seventy-two normal dogs were used in these experiments. At operation a loose ligature was placed around the circumflex branch of the left coronary artery close to its origin. Twenty-four hours later, occlusion was effected by traction on the loose ends of the ligature. Three groups of experiments were carried out using Demerol, ergotamine tartrate, and dihydroergotamine. In addition, the coronary arteries of eight dogs were ligated without the use of drugs, as a check on technique and the mortality rate in conscious dogs. Except in the control animals, the drugs were given before the ligation. Electrocardiograms were taken before and after the administration of the drug, before, during, and for thirty minutes after ligation, and then intermittently for some time after the occlusion. An autopsy was performed on all animals that died. "Sudden death," for the purpose of these studies, means death within the first twenty-four hours.

Including the former control series of sixteen dogs reported in a previous study, the mortality for the untreated group was eighteen deaths in twenty-four dogs within the first twenty-four hours, or 75 per cent.

Demerol was given intramuscularly to twelve dogs in doses of 10 mg. per kilogram of body weight, followed by a second injection of 5 or 10 mg. per kilogram intravenously fifteen to twenty-five minutes later. This drug did not afford much protection against cardiac irregularities, tachycardia, and fibrillation following sudden coronary occlusion. The outstanding feature was the rapid onset of ventricular tachycardia, which occurred in eleven experiments and within two to four minutes terminated in fatal ventricular fibrillation in seven of the twelve animals. Only five of the twelve dogs survived the twenty-four-hour period.

Ergotamine tartrate was administered to thirteen dogs. In the first two animals, 0.5 mg. per kilogram of ergotamine tartrate was given intravenously. In view of untoward effects, a dose of 0.25 mg. per kilogram was given to the remaining eleven dogs. Shortly after the intravenous injection of ergotamine tartrate the animals showed marked muscular weakness, most apparent in the limbs. Increased respiration and dyspnea, which in several animals was of an asthmatic nature, were prominent features. Ergotamine tartrate in doses of 0.25 mg. per kilogram was effective in inhibiting the development of ventricular fibrillation and so reduced the "immediate" mortality. A delayed cardiac death, however, occurred twelve to eighteen hours later in 70 per cent of the animals.

Dihydroergotamine (DHE₄₅) was given intravenously, 0.4 mg. per kilogram, to twenty-three animals four to five minutes prior to the occlusion. Although most of the animals appeared slightly unsteady following the occlusion, the general collapse and weakness and toxic appearance that was such a prominent feature in the ergotamine series was not apparent. Clinically, these animals appeared more like the control dogs that survived the immediate effects of the occlusion. Seven of the twenty-three dogs died within the twenty-four-hour period following ligation (30 per cent mortality). Three of these died in ventricular fibrillation within twelve minutes following occlusion (13 per cent mortality). The remaining four died seventeen to nineteen hours after ligation. In comparison with the ergotamine tartrate series, it is apparent that DHE₄₅ was not only similar in its protecting action against the ventricular fibrillation mechanism, but also significantly increased the survival rate.

BELLET.

Szekely, P., and Snaith, L.: *The Heart in Toxemia of Pregnancy*. Brit. Heart J. 9:128. (April), 1947.

This paper is based upon the observations made in nineteen unselected cases of toxemia of pregnancy. The majority of cases were classified as severe, the criteria being subjective symptoms, such as headache, vomiting, and visual disturbance, and objective findings, such as height of blood pressure, edema, albuminuria, and the occurrence of eclamptic convulsions.

In the present series, a total of seven patients (37 per cent) were thought to have significant changes in the heart; two showed clinical changes only, four showed electrocardiographic changes only, and one showed clinical and cardiographic evidence of cardiac involvement. The electrocardiographic changes were indicative of myocardial damage in at least five cases, because they occurred in both standard and chest leads, and persisted for sometime after delivery, so that the alteration in the anatomical position of the heart during pregnancy could be excluded as a causative factor. The changes in the heart appear to be temporary, but their duration varies considerably. The changes may not only persist for some time after delivery, but may become greater in the post-partum period.

The observations of the authors indicate that gross cardiac enlargement is not a feature of pure "toxemic" cardiac lesion, irrespective of the presence or absence of cardiac failure. Only one of the cases showed enlargement of the left ventricle. If gross cardiac enlargement is present, it probably indicates either antecedent hypertension or heart disease which is not "toxemic" in origin. There is nothing to suggest that pericardial effusion is present in toxemia or pregnancy to account for the electrocardiographic changes or the heart failure. Toxemia of pregnancy is an acute vascular disorder; in this respect, it closely resembles acute glomerulonephritis.

Although convincing proof is still lacking of direct damage to the myocardial vessels in toxemia of pregnancy, in the light of the clinical and anatomic findings, the possibility of struc-

tural damage to the small branches of the coronary arteries cannot be excluded with certainty. The true significance of the observations presented in this paper is their demonstration that cardiac involvement is not uncommon in toxemia of pregnancy. The authors believe that some of the cases of acute ante-partum or post-partum cardiac failure of undetermined etiology may be instances of toxemia even if the recognized signs of the latter condition are not convincingly present; and that some of the cases of vascular collapse known as "obstetric shock" may be instances of true toxemia.

BELLET.

Acosta, F. R.: Ayerza's Disease. *Rev. cubana de cardiología*. 65:00 (April), 1947.

Three factors must be present in the pathogenesis of Ayerza's disease:

(1) Primary sclerosis of the fine- and middle-sized branches of the pulmonary artery with resulting hypertension of the lesser circulation. (2) Hypertrophy and dilatation of the right ventricle with ultimate right-sided failure. (3) Extensive pulmonary lesions, consisting of fibrosis, emphysema, and bronchitis. These alveolar lesions produce hypoventilation and irregular gaseous exchange which result in decreased oxygen saturation and increased carbon dioxide content of the arterial blood, and thereby produce the intense cyanosis and dyspnea which characterize the disease and give its victims the name of "black cardiacs."

GOLD.

Binet, L., and Burstein, M.: Action of Carbon Dioxide on the Tonus of Peripheral Vessels. *Compt. rend. Soc. de biol.* 141:488 (May), 1947.

The circulatory effects of breathing various concentrations of carbon dioxide were studied in the perfused foot of the dog. It was found that hypercapnea caused an intense peripheral vasoconstriction which persisted after section of the four depressor nerves. Hypocapnea was accompanied by an often marked degree of peripheral vasodilatation. The direct action of carbon dioxide on the peripheral vessels appeared to be insignificant.

LAPLACE.

Charlier, R., and Philpott, E.: Hypotension in the Right Ventricle During Occlusion of the Carotid Arteries. *Compt. rend. Soc. de biol.* 141:531 (May), 1947.

Observations were made of the effect produced by occlusion of the common carotid arteries on the pressure in the right ventricle. The experiments were performed on anesthetized dogs. A catheter attached to a manometer was inserted into the right ventricle by way of the right external jugular vein. The inertia of the system was such that only the pressure during diastole was recorded, i.e., the venous filling pressure. Cardiac output, arterial pressure, and peripheral venous pressure were also measured.

It was found that occlusion of the common carotid arteries, irrespective of whether or not the vagi were intact, caused a rapid, sustained increase in right intraventricular pressure. Release of the carotid occlusion was followed by a slow fall of pressure to the previous level. The acceleration of pulmonary blood flow which accompanied occlusion of the carotid arteries was attributed to the increased pressure in the right ventricle.

LAPLACE.

Vazquez, J. O., Montero, J. C., and Gonzales, P. P.: Transient Right Bundle Branch Block Following Thoracoplasty. *Rev. españ. de cardiología*. 1:246 (May), 1947.

A 33-year-old woman had right bundle branch block for at least seven months following a left-sided thoracoplasty with resection of the first five ribs. Nine months after the operation a normal record was obtained. No other evidence of cardiovascular disease was present. Only one electrocardiogram taken before, one seven, and one nine months after the operation were available.

HECHT.

Tum Suden, Caroline: Effect of Adrenocortical and Sympathicoadrenal Factors on the Cardiovascular Sensitivity to Potassium in the Rat. *Am. J. Physiol.* 149:589 (June), 1947.

Ergotamine tartrate increased about threefold the susceptibility of intact rats to repeated injections of potassium chloride, as evidenced by circulatory collapse. Moderate deficiencies of adrenocortical activity favor a potassium-induced circulatory collapse by permitting a more rapid rise in extracellular potassium, whereas inactivation of adrenergic mechanisms by sympatholytic agents may sensitize the cardiovascular system of the rat to potassium at low values. The combination of both dysfunctions produced an acute susceptibility to potassium. The increased susceptibility of ergotamine-treated rats to potassium was further enhanced by histamine but histamine itself had no appreciable effect.

BERNSTEIN.

Eckenhoff, J. E., Hafkenschiel, J. H., Landmesser, C. M., and Harmel, M.: Cardiac Oxygen Metabolism and Control of the Coronary Circulation. *Am. J. Physiol.* 149:634 (June), 1947.

The original purpose of these experiments was to examine the thesis that the coronary vessels, like the cerebral vessels, possess an effective intrinsic control in relation to the metabolic requirements of the tissue. The data do not afford any evidence as to the mechanisms involved in these adjustments, whether nervous or chemical, and, if the latter, the exact identity of the chemical factors. From the demonstration that anoxemia, excess hydrogen ions, acetylcholine, and epinephrine are all capable of dilating the coronary arteries, it is concluded that no one chemical agent need be selected as being solely or predominately involved; the effect is more likely to be due to the consensual and simultaneous effects of all the demands and products of cardiac metabolism. The authors were not able to demonstrate any effective vasomotor control over the coronary circulation under the experimental conditions.

When the blood pressure was increased, cardiac output and cardiac work fell, while cardiac oxygen consumption increased, with consequent decrease in efficiency. When cardiac output was primarily increased, cardiac work, cardiac oxygen consumption, and cardiac efficiency all increased, even though the blood pressure rose concurrently. When, as a result of anoxemia, cardiac output fell while blood pressure and oxygen consumption remained unchanged, cardiac efficiency decreased. All this suggests that a fall in blood pressure without a decrease in cardiac output, such as may occur in spinal anesthesia or circulatory collapse, may not be as ominous as it is generally believed to be.

The heart appears to be safeguarded against anoxia by three mechanisms: (a) decreased tonus in the coronary vessels; (b) diversion of a relatively larger fraction of total cardiac output to the coronary circulation; (c) decreased cardiac work, perhaps associated with increased cardiac efficiency consequent to the fall in aortic pressure.

BERNSTEIN.

Karpovich, Peter V.: Breath Holding as a Test of Physical Endurance. *Am. J. Physiol.* 149:720 (June), 1947.

Since many previous investigators had considered breath holding as a test of cardiorespiratory fitness, it was decided to find the relationship between breath holding and standard physical activities which place considerable demands upon the cardiorespiratory function. As determined, the coefficients of correlation between the breath holding tests and the treadmill running time and the Harvard test score are not statistically significant. For this reason, breath holding tests cannot be used for prediction of endurance. The time the breath can be held apparently measures the ability to withstand the discomfort caused by breath holding and in no way assesses physical fitness.

BERNSTEIN.

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Program of the Twenty-First Scientific Sessions of the American Heart Association, June 18-19, 1948, North Ballroom, Stevens Hotel, Chicago, Ill.

Essayists, except the George Brown Memorial Lecturer, will be restricted to fifteen minutes; discussors, to three minutes. Each discussor will speak from the rostrum after a notation including his name, address, and the presentation to be discussed has been handed to the secretary. Questions lacking general interest should be directed to essayists privately after discussion has been completed. Each essayist must leave his manuscript with the presiding officer. All manuscripts will be considered the property of the American Heart Association, and will be forwarded to the Editor of the AMERICAN HEART JOURNAL for consideration for publication in that Journal.

First Session 2:00 P.M., Friday, June 18
Second Session 9:00 A.M., Saturday, June 19
Third Session 2:00 P.M., Saturday, June 19

The following is the program of papers to be read to the Scientific Sessions:

- "George Brown Memorial Lecture," by Edgar V. Allen, Mayo Clinic, Rochester, Minn.
- "A Clinical Study of Subacute Bacterial Infection Confined to the Right Side of the Heart or the Pulmonary Artery," by Paul S. Barker, University of Michigan Medical School, Ann Arbor, Mich.
- "Plasma and Blood Infusion Following Myocardial Infarction," by John J. Sampson and Isidore M. Singer, Harold Brunn Institute for Cardiovascular Research, Mt. Zion Hospital, San Francisco, Calif.
- "Report of the Committee for the Evaluation of the Use of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction," by Irving S. Wright, Chairman, New York, N. Y.
- "Animadversions Upon the Nature and Cure of the Dropsy; Particularly on the Optimal Intake of Water for Edematous Cardiac Patients," by Ferdinand R. Schemm, Great Falls Clinic, Great Falls, Mont.
- "Surgical Treatment of Aneurysms of the Aorta and Its Large Branches," by Gerald H. Pratt, New York Hospital, New York, N. Y.
- "The Diagnosis of Interauricular Septal Defect," by Richard S. Cosby and George C. Griffith, Los Angeles County General Hospital, Los Angeles, Calif.
- "Production of Arteriosclerosis in Dogs by Cholesterol and Thiouracil Feeding," by Alfred Steiner, Forrest E. Kendall, and Margaret Bevans, First (Columbia) Division, Goldwater Memorial Hospital, New York, N. Y.
- "Arterectomy in the Treatment of Ischemic Neuritis Following Arterial Occlusion," by Norman E. Freeman, Frank H. Leads, and Richard E. Gardiner, University of California Medical School, San Francisco, Calif.
- "Differentiation of the Change in the Q-T Interval of the Electrocardiogram in Hypocalcemia and Hypopotassemia," by A. Carlton Ernstene and William L. Proudfit, Cleveland Clinic, Cleveland, Ohio.
- "Studies on the Circulation With the Use of Radio-Active Tracers," by Myron Prinzmetal, Cedars of Lebanon Hospital, Los Angeles, Calif.

- "The Water Tolerance of the Hypertensive Patient: Its Relation to Operability," by Geza de Takats and Edson F. Fowler, University of Illinois College of Medicine, Chicago, Ill.
- "Clinical Studies on Twenty-One Cases of Coarctation of the Aorta," by M. J. Shapiro, Children's Heart Hospital, Minneapolis, Minn.
- "Normal and Impaired Function of the Superficial Veins," by J. B. Hickam and R. P. McCulloch, Duke University School of Medicine, Durham, N. C.
- "Pathology of the Pulmonary Arterioles in Aortic Coarctation Associated With Patent Ductus Arteriosus," by Jesse E. Edwards, Howard B. Burchell, and Norman A. Christensen, Mayo Clinic, Rochester, Minn.
- "Studies of Arterial Oxygen Saturation in Patients With Suspected Arterial Hypoxemia Utilizing a Modified Oximeter," by J. E. Jeraci, G. E. Montgomery, and E. H. Wood, Mayo Clinic, Rochester, Minn.
- "Biomicroscopy of Conjunctival Vessels in Hypertension," by Arthur Lack, Travis Winsor, William Adolph, and Walter Ralston, University of Southern California School of Medicine, Los Angeles, Calif.
- "Correlation Between the Decrease in Coronary Flow and the Electrocardiographic Changes in Progressive Coronary Occlusion," by Rene Wegria, Marcel Seegers, and Richard P. Keating, Presbyterian Hospital, New York, N. Y.

Papers to be read of time permits.

- "Cardiac Effects of Non-Pressor Sympathomimetic Compounds," by M. H. Nathanson, University of Southern California School of Medicine, Los Angeles, Calif.
- "Dissecting Aneurysm of the Aorta in World War II: Clinical and Pathological Study of Eighty-Five Cases," by Vincent J. Seiwert and Ira Gore, Army Institute of Pathology, Washington, D. C.
- "The Pathogenesis of Diastolic Hypertension," by Peter Heinbecker, Washington University School of Medicine, St. Louis, Mo.
- "The Heart in the Terminal State: Effect of Intracardiac Epinephrine," by Edward Massie, Charles H. Huguley, and Hyman S. Stillerman, Washington University School of Medicine, St. Louis, Mo.
- "The Use of Veratrum Viride in the Treatment of Essential Hypertension," by Edward D. Freis, Joseph R. Stanton, and Robert W. Wilkins, Boston University School of Medicine, Boston, Mass.
- "Evaluation of Three Methods for Determining the Rate of Dissipation of Digoxin in Man," by Robert C. Batterman and Arthur C. DeGraff, New York University College of Medicine, New York, N. Y.
- "The Clinical Significance of the U Wave in the Electrocardiogram," by Stephen Elek, L. S. Gottlieb, and George C. Griffith, University of Southern California School of Medicine, Los Angeles, Calif.

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Original Communications

THE EFFECT OF ERGOT DERIVATIVES ON THE CIRCULATION IN MAN WITH SPECIAL REFERENCE TO TWO NEW HYDROGENATED COMPOUNDS (DIHYDROERGOTAMINE AND DIHYDROERGOCORNINE)

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CAPE TOWN, SOUTH AFRICA

ALTHOUGH Dale,⁷ as early as 1906, clearly recognized two active principles in the ergot alkaloids, namely, the direct pharmacologic effect on smooth muscle and the inhibition of sympathetic activity, it was mainly for the former that ergot preparations found widespread therapeutic application, particularly in obstetrical practice. The principle responsible for the inhibition of sympathetic activity, however, remained more of pharmacologic and physiologic interest except, perhaps, in the treatment of migraine where this component may play its part.¹ Recent developments in sympathetic surgery, particularly with regard to essential hypertension, which implicate the sympathetic nervous system, if not in the genesis then at least in the maintenance of the raised blood pressure, have focused attention anew on sympathicolytic drugs.¹⁴ By adding a purely sympathicolytic drug to the physician's armamentarium, it may be possible to offer some hope of relief to the vast number of cases of neurovascular disorders, and perhaps replace splanchnicectomy by medicinal measures in certain cases of hypertension. It is the purpose of this paper to investigate two new (hydrogenated) derivatives of ergot (dihydroergotamine and dihydroergocornine) as to their action on the cardiovascular system with particular reference to their sympathicolytic properties, and to compare their action with that observed following the administration of ergotamine tartrate (Gynergen).

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THE DRUGS

Dale's original experiments were carried out with crude ergot extracts and ergotoxine. The latter was isolated in 1906 by Barger and Carr,² and by Kraft.²³ There was no doubt that ergotoxine was not a pure substance and in 1918, Stoll³⁶ isolated ergotamine which, pharmacologically, was practically indistinguishable from ergotoxine⁹ but one-half as toxic.²⁵ Ergotamine quickly found widespread therapeutic application because of its prompt and powerful effect on the uterine muscle. Its beneficial effect in migraine was first recognized by Maier²⁶ and has since become one of the main indications in the usage for this drug. In 1935, a new ergot alkaloid was independently isolated by Stoll and Burckhardt,³⁸ Dudley and Moir,¹⁰ Thompson,⁴⁴ and Kharasch and Legault,²¹ which the various workers termed ergobasine, ergometrine, ergostetrine, and ergotocine, respectively. In 1936, a joint report by the teams concerned²² established the chemical identity of the respective principles. The new drug had a marked and almost selective oxytocic action on uterine muscle. During the same period, Smith and Timmis³⁴ (1932) and Jacobs and Craig (1935)¹⁹ succeeded in identifying lysergic acid as the principal and characteristic constituent of all ergot alkaloids, and in 1938 its formula was definitely established by Jacobs and Craig.²⁰ In the same year, Stoll and Hofmann³⁹ achieved the synthesis of ergobasine.

Three additional alkaloids were isolated from ergotoxine by the same authors⁴⁰ in 1943, one of which had, however, already been known as ergocristine. The other two they termed ergokryptine and ergocornine. These three alkaloids were different from each other in both their chemical and physical properties. By 1943, therefore, the following alkaloids of the ergot group were known: ergotamine, ergobasine, ergokryptine, ergocornine, and ergocristine. Lysergic acid being readily transformable into its isomer, isolysergic acid, it follows that each of the various ergot alkaloids has its isomer which, however, is pharmacologically inert. It is the levorotatory of the two compounds which is pharmacologically active. All active compounds except ergobasine, which is purely oxytocic, contained both active principles; that is the direct effect on smooth muscle and the sympathicolytic component.

The next important step came from Stoll and Hofmann⁴¹ when in 1943 they demonstrated that well-defined compounds of the ergot alkaloids could be obtained by hydrogenating the readily reducible double bond of their lysergic acid. In this way they produced four new compounds: dihydroergotamine, dihydroergocristine, dihydroergocornine, and dihydroergokryptine. These hydrogenated derivatives were less toxic and less emetic than the original alkaloids and it was found that hydrogenation increased the sympathicolytic effect and diminished or abolished the direct action on smooth muscle.^{30,31,37,6,33,35}

It is this aspect, in particular, which makes the new compounds of special interest and which stimulated this study for which the following substances were available: ergotamine tartrate (Gynergen), dihydroergotamine (DHE 45), and dihydroergocornine (DHO 180).*

*The preparations were made available through the courtesy of Prof. E. Rothlin, Sandoz Limited, Basle, Switzerland.

METHODS AND MATERIAL

Continuous records of the peripheral circulation were obtained by means of the Goetz optical digital plethysmograph described in detail elsewhere.¹¹⁻¹³ This sensitive method not only allows correct registration of the height of the volume pulse, but also calculation of the arterial inflow at any one moment by means of the so-called venous congestion test.¹³ As is seen in various tracings, the respiration was continuously recorded simultaneously with the plethysmogram, and the skin temperature of one or more digits measured by means of a mirror galvanometer and thermocouples. The blood pressure was taken at regular intervals by clinical methods and the heart rate, of course, was available from the plethysmogram. Electrocardiographic tracings were taken at various intervals in many individuals. The drugs were given either by continuous intravenous infusion or by instantaneous intravenous injection, the mode of administration being indicated on every figure or chart. For intravenous infusion two drips were set up, connected via a two-way tap to the needle, and by merely turning the tap the drug could be administered or withheld without the patient being aware of it. Intravenous infusion was preferred because the interference resulting from the psychical trauma accompanying puncture of the vein could be avoided by administering saline for a considerable time before the drug was given. The drugs were tested on twenty-four subjects. In some of them, sympathectomies on one or more extremities had been carried out for various reasons, as stated in the legends of the respective figures. Additional information was available from twenty-four hypertensive patients who had been given the drugs for investigations reported elsewhere.⁵ All patients used for this study reclined comfortably on a bed, usually wearing a suit of pajamas. The tests were carried out after a rest of thirty to sixty minutes. By that time, the volume records showed a minimum of spontaneous fluctuations in peripheral blood flow. If required, reflex vasodilatation was obtained by immersion of one or two extremities into a specially built tank containing water of 44 to 45° C., and covering the subject with blankets in order to prevent the dissipation of heat. An immersion heater connected in series with a thermostat and a stirring propeller were fixed in the tank to keep the water temperature constant at that level.

RESULTS

The Effect of Gynergen on the Circulation in Normally Innervated and Sympathectomized Limbs.—Intravenous injection of Gynergen produces inconstant and complex changes in the peripheral circulation, depending on the dose and because of the conflicting action of the two active constituents, that is, the direct constrictor effect on smooth muscle and the sympathicolytic (vasodilator) principle. The effect in the normally innervated limb is thus the result of the interaction of both these components, and therefore, both constriction or dilatation may be obtained depending entirely upon the dose and the preponderance of the action of one or the other component. This, in turn, depends on the state of the circulation (the vasomotor tone) in that particular subject at the time of

the injection. Obviously, if at the time of injection the vessels are dilated, sympathetic paralysis cannot be demonstrated. Vice versa, to demonstrate constriction the vessels should first be dilated. With vessels neither fully dilated nor fully constricted, Gynergen more often than not causes transient dilatation followed by prolonged constriction. However, occasionally the vessels, once

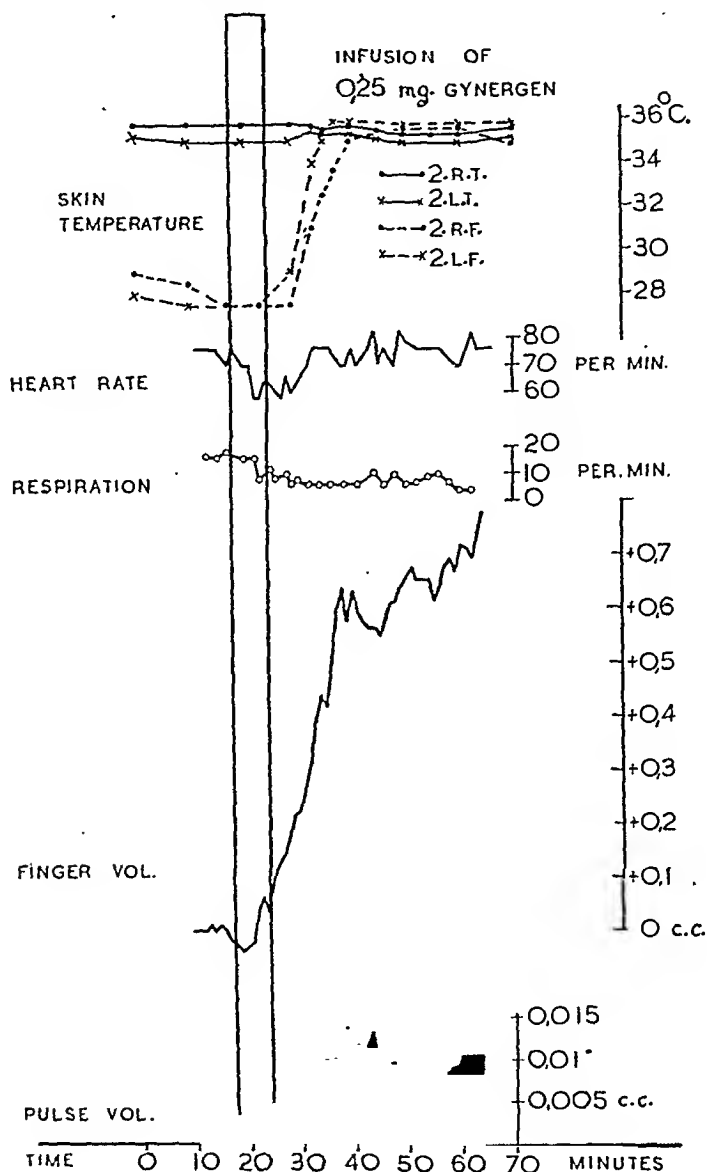


Fig. 1.—The effect of 0.25 mg. Gynergen (ergotamine tartrate) on the skin temperatures, heart rate, respiration, digital volume, and pulse volume (second left finger), all simultaneously recorded. The leg had been sympathectomized for ulcers in 1943. The upper extremities were normal. (Mrs. S. W.)

initiated into dilating, remain dilated thereafter, particularly after small doses (Fig. 1). In Fig. 1 a small dose (0.25 mg.) of Gynergen was given by intravenous drip over a period of ten minutes, and the skin temperature of four digits, heart rate, respiration, finger volume, and pulse volume were continuously recorded for the next hour. Before the administration, the vessels of the upper extremi-

ties were under a high vasomotor tone. Following the infusion, there was a definite and lasting increase in digital blood flow, as indicated by a rise in pulse volume from 0.003 c.c. to about 0.01 c.c. and a rise in finger volume by about 0.7 c.c. within twenty minutes. The skin temperatures of the fingers rose simultaneously from 28° to 35° C., while those of the sympathectomized and consequently dilated toes actually showed a slight drop. These findings are readily explained as resulting from the sympathicolytic effect of the drug. Fig. 2,A is an example of a case in which dilatation was less marked and followed by

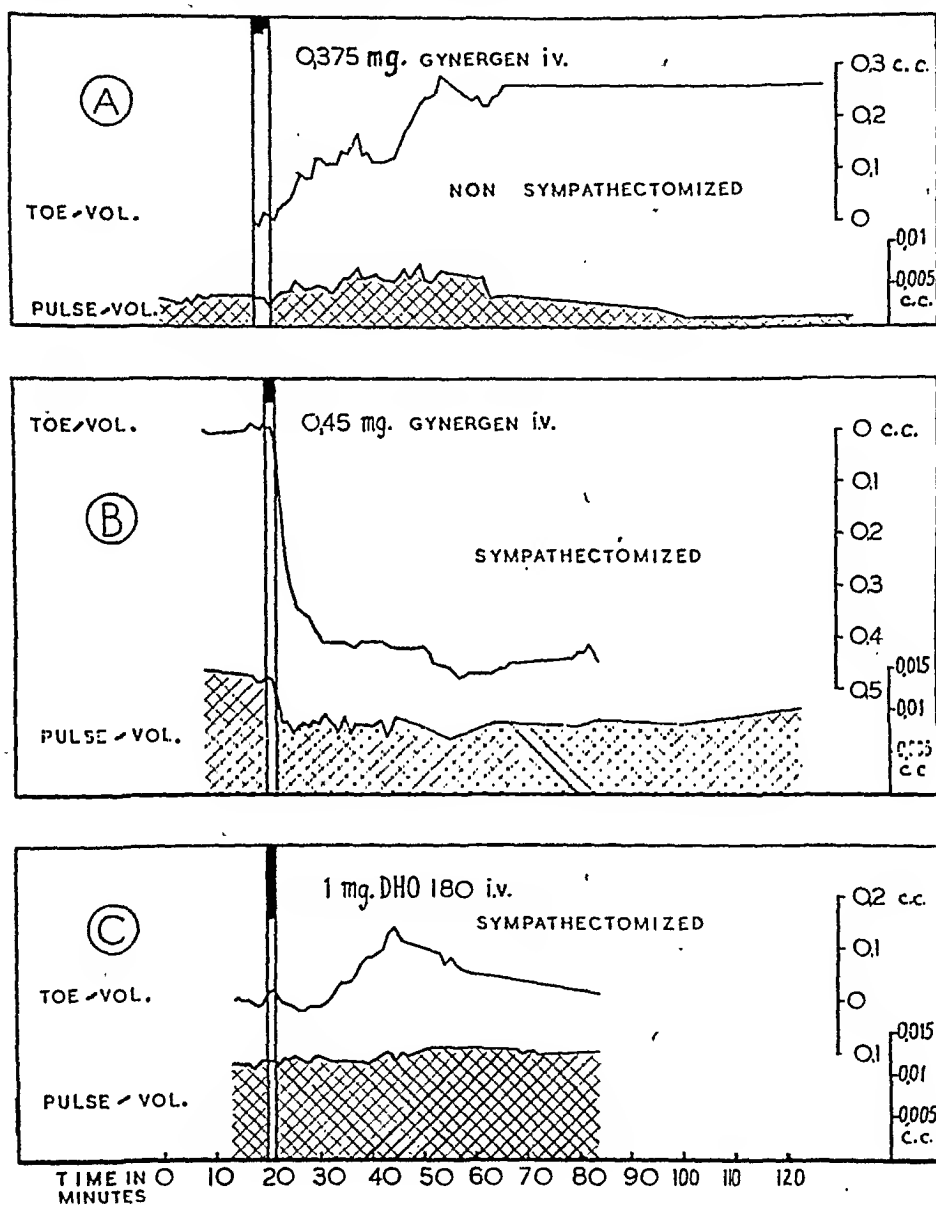


Fig. 2.—The effect of Gynergen on the peripheral blood flow (first right toe) before and fifteen days after lumbar sympathectomy for chronic crural ulcer as compared with the effect of DHO 180 on the sympathectomized limb of the same patient. For explanation, see text.

lasting constriction. The injection resulted in only a slight rise in pulse volume and thereafter full constriction of the peripheral vessels was recorded, the pulse volume becoming practically unregistrable after eighty minutes. The digital volume, too, showed only a slight increase (0.25 c.c.) within the first half hour,

and the skin temperatures did not change significantly. It is our experience that the sympathicolytic effect of the drug, that is, peripheral vasodilatation, is more readily recorded with the smaller doses (± 0.25 mg.) but that in larger doses peripheral constriction becomes more prominent, completely overshadowing any possible vasodilator effects of the sympathicolytic principle.

A detailed account of the changes in the pulse volume charted in Fig. 1 demonstrates that the vessels were almost fully constricted before injection and the pulse volume consequently registered only 0.0025 cubic centimeter. Ten minutes after the commencement of the intravenous drip, no changes in pulse volume were as yet recorded, although the respiration which before was regular (18 per minute) had already become markedly slowed and irregular. Fifteen minutes later a definite dilatation was recorded, the pulse volume having increased to 0.008 cubic centimeter. After a further twenty minutes the pulse volume was still the same and the respiration still depressed and irregular.

If the same dose of Gynergen (0.25 mg.) is given to the same patient but the circulation in the sympathectomized limbs* recorded; the same effect is always registered: definite vasoconstriction.

Fig. 2, A and B, is of particular interest since it illustrates the vascular reaction to Gynergen in one and the same digit before and after sympathectomy. Note the marked, immediate fall in pulse volume from 0.012 c.c. to 0.006 c.c. in the sympathectomized limb and the reduction in digital volume by 0.45 c.c., as against the transient dilatation before operation. Both digital volume and pulse volume remained at this low level in the sympathectomized limb for the following two hours during which the circulation was recorded.

The cuttings from the original film (Fig. 3) give a very clear picture of the powerful constriction obtained. Two minutes after the injection the pulse volume had already decreased from 0.012 c.c. to 0.008 c.c. and after five minutes it registered 0.006 c.c. only. Accompanying the reduction in pulse volume there was a steep fall in digital volume. The respiration was not markedly affected in this patient, although the dose was larger than in the patient concerned in Fig. 1. It should also be noted that, contrary to the reaction in the normal subject, puncture of the vein did not produce any vasomotor reaction of either pulse volume or digital volume, giving proof of the completeness of the denervation.

The effect of Gynergen in the sympathectomized limbs is obviously due to the pharmacologic action of the drug on the vessel wall, resulting in vasoconstriction. In none of our subjects did we record vasodilatation in a sympathectomized limb at any time and with any dose, indicating clearly that for its production the integrity of the sympathetic pathways is essential.

By testing the circulatory effect of the drug in both a normal and a sympathectomized extremity, the two components, that is, the direct pharmacologic

*In all patients used for this study the sympathectomized limbs had been tested by various methods and the complete sympathetic denervation substantiated.

action and the sympathicolytic effect, can be separated and the direct acting principle can be demonstrated in its pure form. This procedure was followed for evaluating the effects of both dihydroergotamine and dihydroergocornine in the cases to be reported.

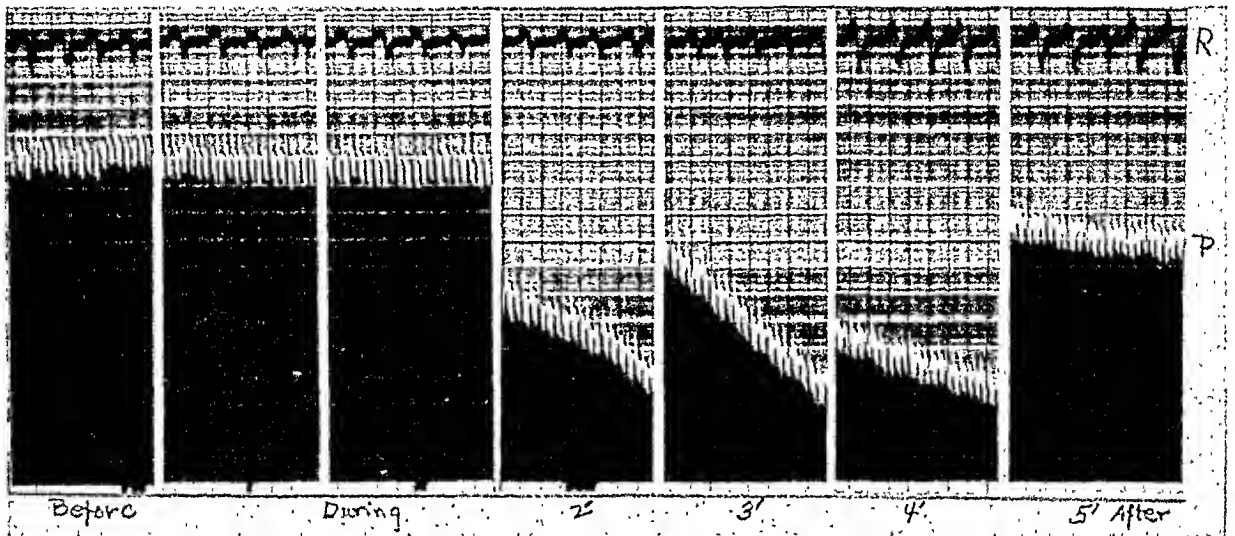


Fig. 3.—The effect of 0.45 mg. Gynergen on the respiration (R) and the plethysmogram (P) of a sympathectomized limb (first right toe), same test as Fig. 2, B. Note the drop in digital volume and pulse volume. The former has been adjusted several times between the cuttings.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Effect on Blood Pressure and Heart Rate: Without going into any detail, we should like to record that Gynergen invariably and in all doses caused a rise in systolic and diastolic blood pressure which varied between 10 and 40 per cent, with an average of 20 per cent, while the pulse rate tended to decrease by 10 to 15 per cent.

The Effect of Dihydroergotamine (DHE 45) on the Peripheral Circulation.—The effect of dihydroergotamine (DHE 45) on the peripheral circulation is essentially the same as that of ergotamine tartrate. Although Stoll³⁷ claims that dehydrogenation abolishes the direct action of the ergot alkaloids on smooth muscle, dihydroergotamine, like its original compound, ergotamine, in our experiments still caused marked constriction in the sympathectomized extremity. In Fig. 4 we reproduce the effect of an intravenous injection of 0.3 mg. dihydroergotamine on skin temperature, blood pressure, heart rate, digital volume, pulse volume, and rate of blood flow (as calculated by the venous congestion test, Goetz¹³), all simultaneously recorded in a patient in whom all four limbs had been sympathectomized. The chart is self-explanatory. There was an instantaneous diminution in peripheral blood flow as expressed by a drop in digital volume and pulse volume. The rate of blood flow actually diminished by about 60 per cent, while the blood pressure simultaneously rose from 115/80 to 140/90 and the heart rate dropped from 85 to 60 beats per minute. A detailed account of the effect of dihydroergotamine on the pulse volume, heart rate, and respiration is

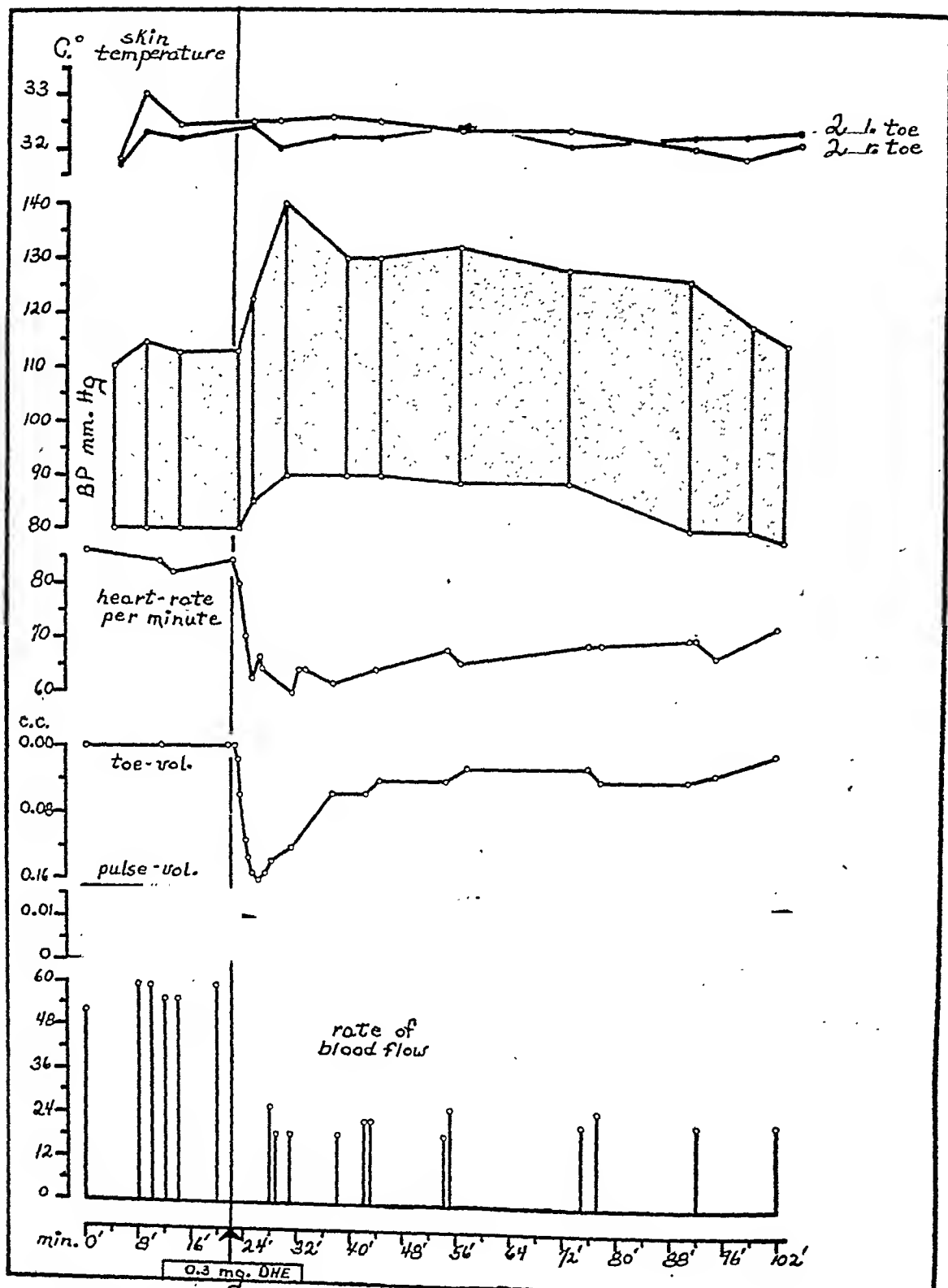


Fig. 4.—The effect of intravenous injection of 0.3 mg. dihydroergotamine (DHE 45) on the skin temperatures, blood pressure, heart rate, digital volume (first right toe), pulse volume, and rate of blood flow, all simultaneously recorded in a patient in whom all four limbs had been sympathectomized for Raynaud's disease. (Left upper, Jan. 21, 1944; right upper, Feb. 17, 1944; double lumbar sympathectomy, March 9, 1944.) For explanation see text.

available from Fig. 5. Before the injection, the pulse volume reached 0.018 cubic centimeter. Ten minutes after the injection, however, it was only 0.01 c.c., and the heart rate had dropped from 85 to 60 per minute during the same period. The changes occurring in the rate of blood flow, as calculated from venous congestion tests, are illustrated in Fig. 6. Before the injection the rise

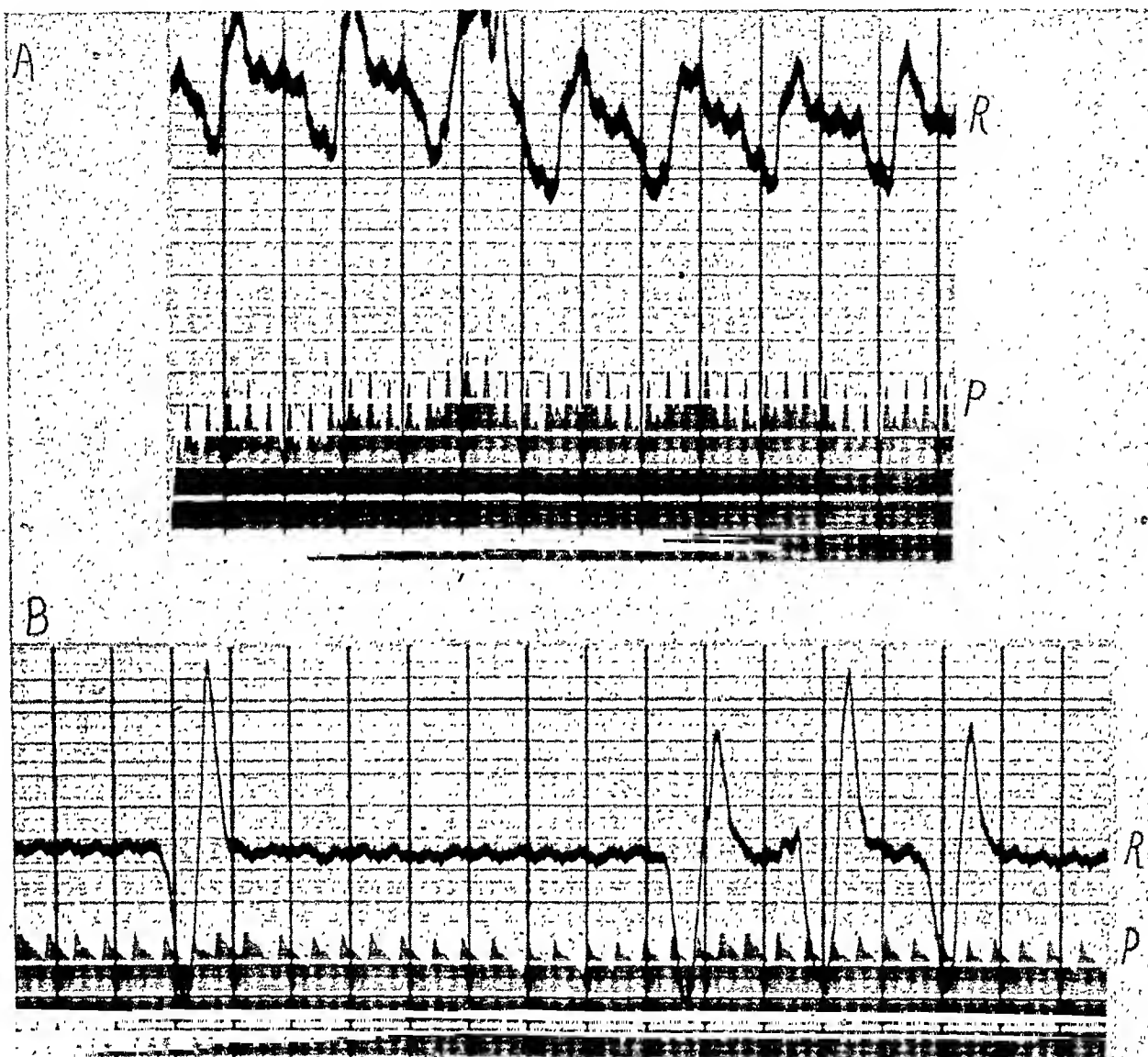


Fig. 5.—Cuttings of the plethysmographic records of the test charted in Fig. 4, showing respiration and pulse volume (first right toe) of sympathectomized limb before, and following, the injection of 0.3 mg. dihydroergotamine (DHE 45). Note slowing of pulse, vasoconstriction, and irregularities in respiration after DHE.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Reduction of original tracings to 2/3.

in digital volume on venous congestion amounted to about 0.07 c.c. during two seconds (Fig. 6,A). Ten minutes after the injection (Fig. 6,B) it had dropped to slightly more than 0.02 cubic centimeter. When calculating the rate of blood flow according to the formula previously given,¹³ this fall corresponds to a

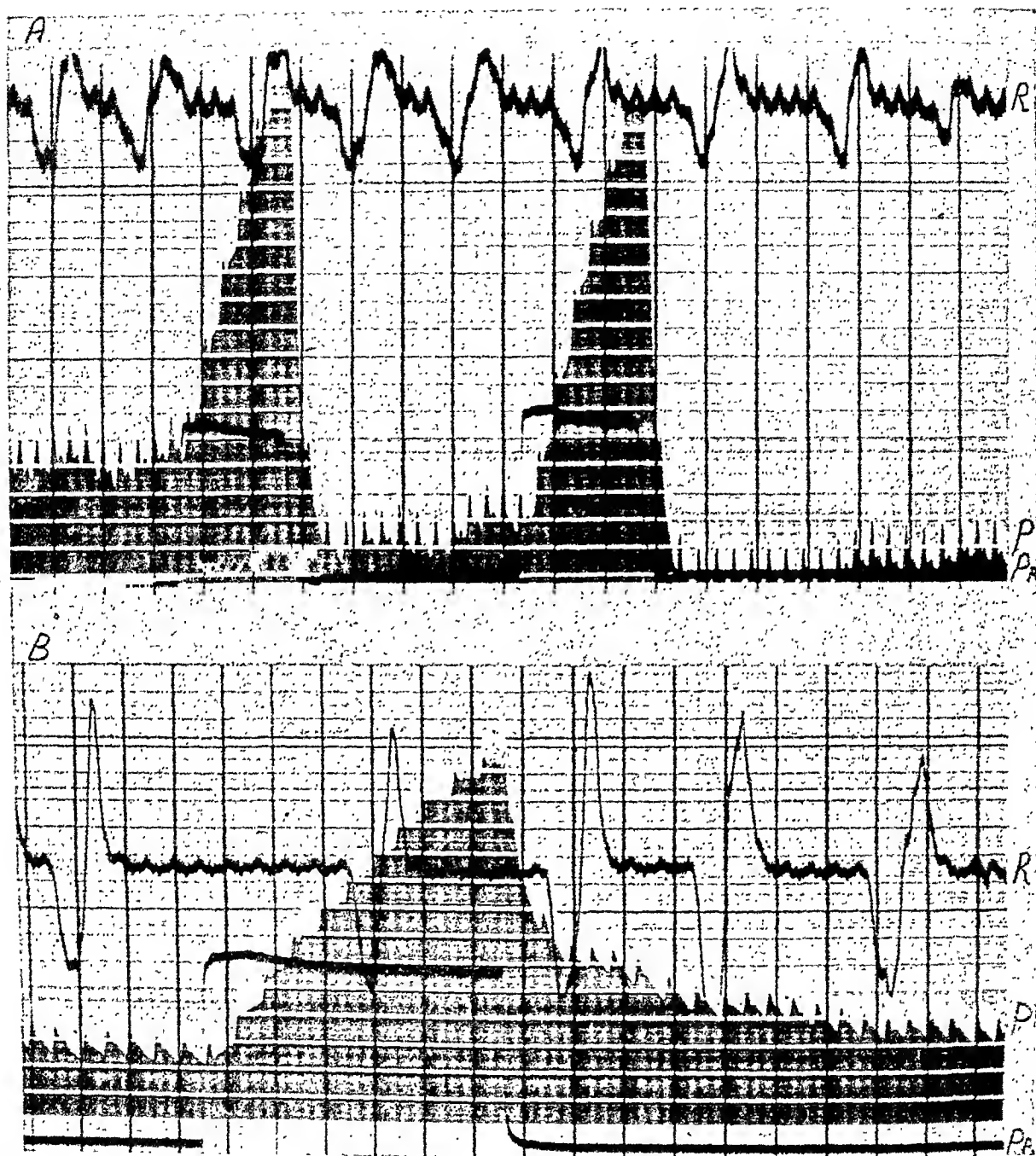


Fig. 6.—Venous congestion tests before and after 0.3 mg. dihydroergotamine in the same patient from whom Figs. 4 and 5 were obtained. *A*, Venous congestion before DHE. *B*, Five minutes after the injection of 0.3 mg. DHE. Note the reduction in arterial inflow, the diminution in the height of the pulse volume, and the irregularities in respiration.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Abbreviations: *R* = Respiration, *P* = plethysmogram, and *PR* = pressure for venous congestion test.

Reduction of original tracings to 2/3.

drop from 60 c.c. per minute for 100 c.c. of tissue to about 20 c.c. per minute for 100 c.c. of tissue. The changes in respiration are well illustrated in both Figs. 5 and 6.

This diminution in peripheral blood flow is not very transient. It takes at least eighty minutes for the blood pressure to return to normal, while the rate of blood flow and heart rate are not back to the original level even after that period. The effect of dihydroergotamine on the peripheral circulation has been the same in the sympathectomized limbs of all subjects, irrespective of the dose, and in Fig. 7 the reaction of the pulse volume and digital volume to the intravenous injection of 1.0 mg. dihydroergotamine in another patient leaves no doubt as to the constrictor effect of this drug on the peripheral vessels. The pulse volume decreased rapidly from 0.012 c.c. to 0.005 c.c. as the drug was being



Fig. 7.—The effect of DHE (1.0 mg. intravenously) on the respiration and plethysmogram (first left toe) in a sympathectomized limb (double lumbar sympathectomy on Oct. 31, 1944, for crural ulcers). The digital volume has been adjusted several times between the cuttings following the injection of the drug.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

injected, and remained at the latter value thereafter. The toe volume, in consequence, decreased sharply. In Fig. 7, both pulse volume and digital volume reached their lowest values after about four minutes. The respiration of this subject was not markedly affected by the injection. In general, larger doses of dihydroergotamine are tolerated, since the drug is definitely less toxic than its original compound, ergotamine tartrate, as has already been stated by Rothlin³⁰ and Stoll.³⁷

Consequently, the effect of dihydroergotamine (DHE 45) on the peripheral circulation in normally innervated limbs is, like that of ergotamine, a mixture of both the direct pharmacologic effect on the peripheral blood vessels and of the paralysis of sympathetic impulses. Therefore, like ergotamine, various reactions are obtained, depending upon the vasomotor tone and upon the dose. However, it appears that the direct pharmacologic action is less marked in this derivative than in the original compound.

As for the effect of dihydroergotamine on the blood pressure in normal subjects, the most common finding in our series was a rise in both the systolic and diastolic blood pressures. However, a definite fall, particularly following a transient rise, has been observed in a number of cases.

The Effect of Dihydroergocornine (DHO 180) on the Peripheral Circulation.—Contrary to the effect of both ergotamine and dihydroergotamine, the response of the peripheral circulation to dihydroergocornine, if present, is always the same, that is, vasodilatation. Fig. 8 illustrates the changes in pulse volume, digital volume, heart rate, and respiration observed after intravenous injection

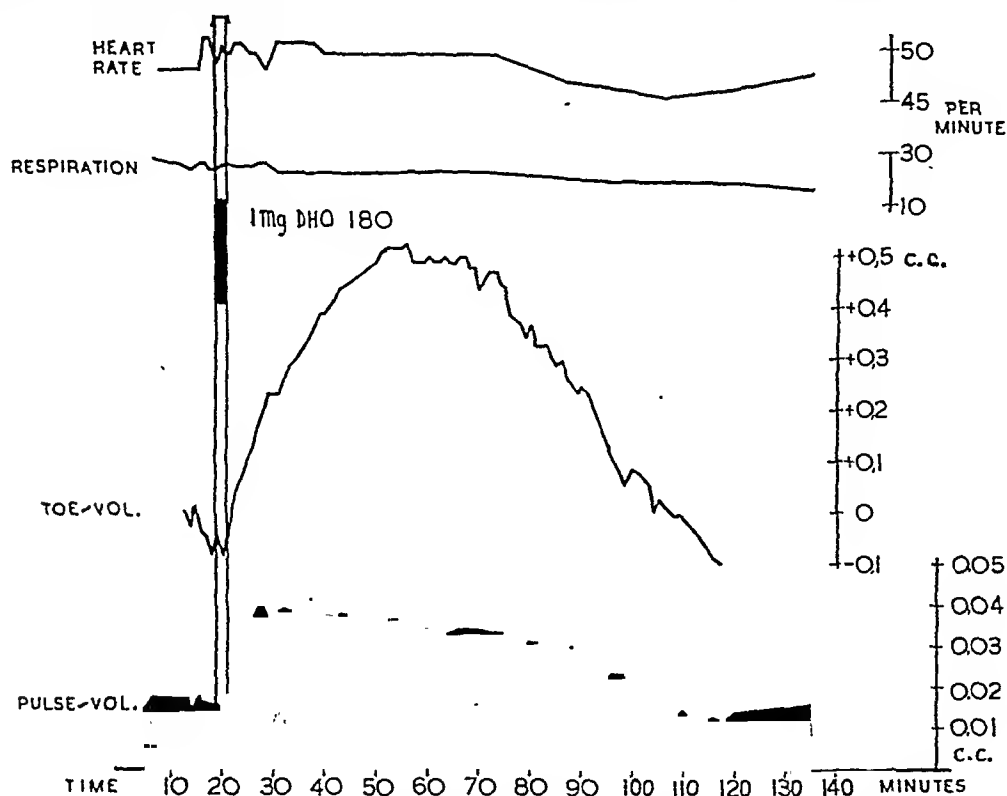


Fig. 8.—The effect of intravenous injection of 1.0 mg. dihydroergocornine (DHO 180) on the peripheral blood flow (first right toe), respiration, and heart rate in a normal subject. For explanation see text.

of 1.0 mg. dihydroergocornine (DHO 180) in a normal individual. Following the injection a marked dilatation was observed, being at its maximum about seven minutes following the injection. The pulse volume rose within a few minutes from 0.012 c.c. to 0.04 c.c., which means that the vascular tone had been completely abolished, and returned to the original height only after about two hours. The toe volume correspondingly increased by 0.5 cubic centimeter. In other subjects, the injection of dihydroergocornine resulted in an increase in the circulation to full vasodilatation level and the vessels remained fully dilated while under observation.

The changes in blood flow following the injection of 1.0 mg. dihydroergocornine are most striking in the cuttings from the original tracing (Fig. 9).

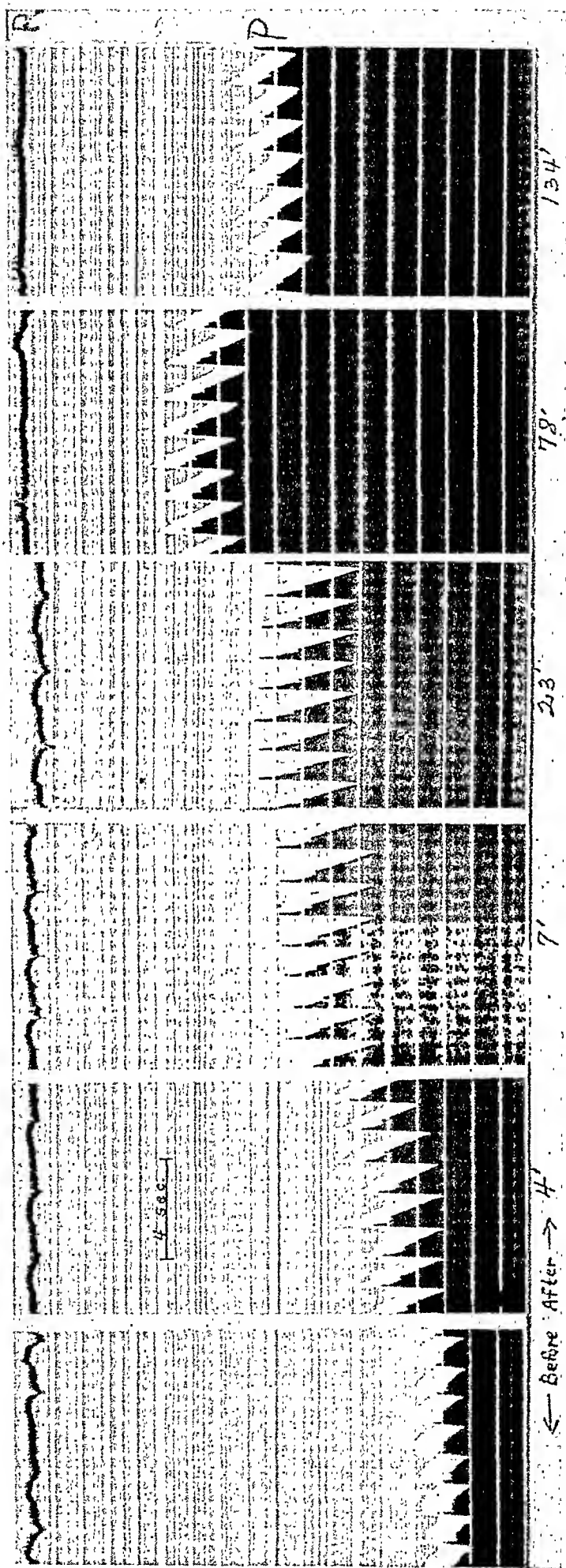


Fig. 9. — Cuttings from the plethysmographic record (first right toe), of the test charted in Fig. 8 (1.0 mg. DHO intravenously). The digital volume has been adjusted several times between the various cuttings.

White horizontal lines = calibration for pulse volume and digital volume. Change from 11ne to line = 0.01 cubic centimeter.

Reduction of original tracings to 2/3.

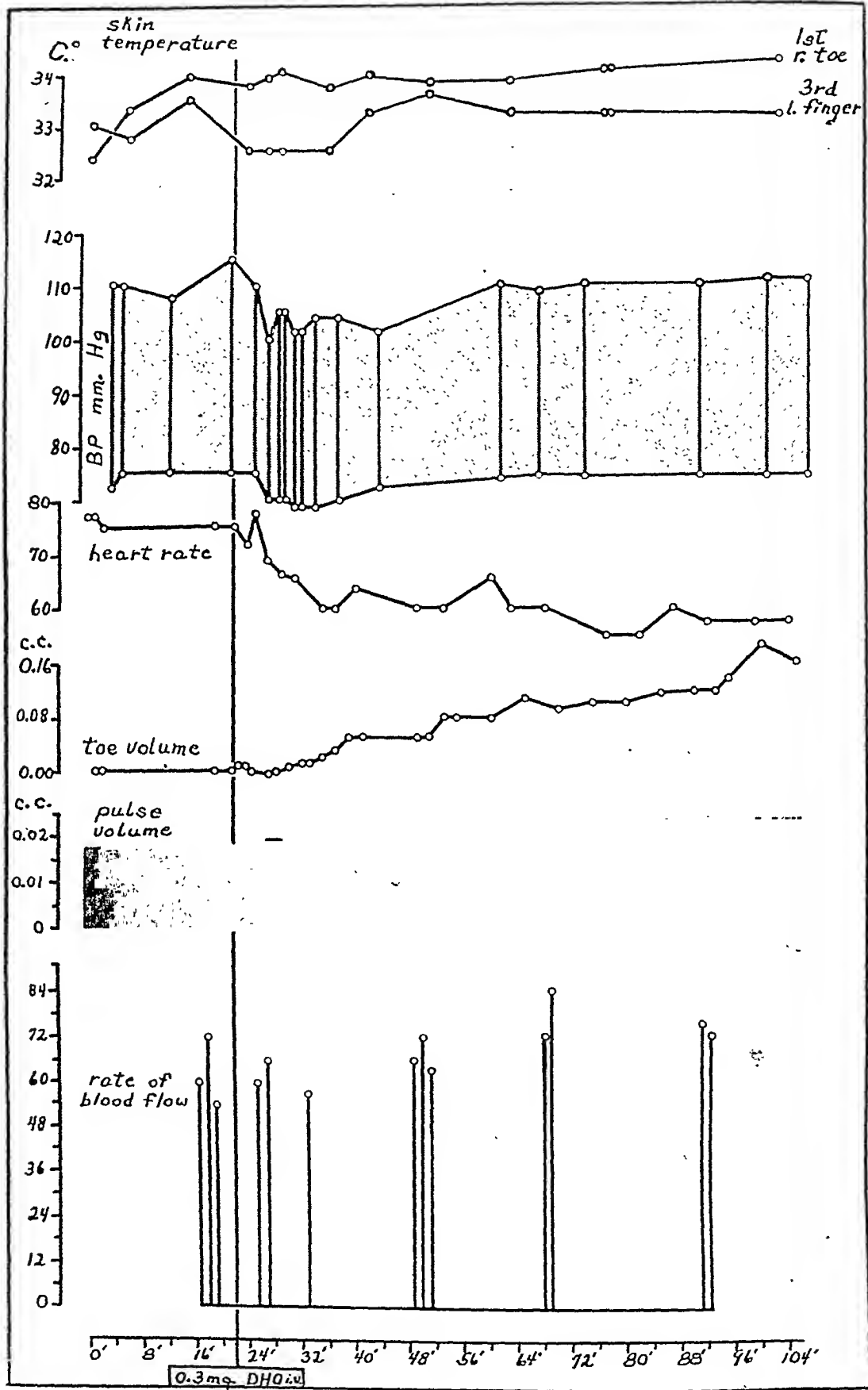


Fig. 10.—The effect of intravenous injection of 0.3 mg. dihydroergocornine (DHO 180) on the skin temperature, the blood pressure, heart rate, toe volume (first right toe), pulse volume, and rate of blood flow, all simultaneously recorded in a patient in whom all four limbs had been sympathectomized for Raynaud's disease (left upper limb, Jan. 21, 1944; right upper limb, Feb. 17, 1944; double lumbar sympathectomy, March 9, 1944). Compare with the effect of DHE in the same subject (Fig. 4). For explanation see text.

Before the injection the pulse volume registered 0.012 cubic centimeter. Four minutes after the injection it had risen to 0.025 c.c. and three minutes later its value was 0.035 c.c., remaining at that level for the next sixteen minutes. Seventy-eight minutes after the injection, the pulse volume was still increased, being 0.02 c.c., and only after two and one-half hours following the injection was the initial level of 0.012 c.c. reached.



Fig. 11.—Cuttings from the original plethysmographic tracing to indicate the increase in pulse volume obtained following 0.3 mg. DHO and charted in Fig. 10. Note also the reduction in heart rate.

White horizontal lines = calibration for pulse volume and digital volume. Change from line to line = 0.01 cubic centimeter.

Ordinates = 2 seconds.

Reduction of original tracings to 2/3.

In the sympathectomized extremity, dihydroergocornine, in contrast to ergotamine and its hydrogenated compound, dihydroergotamine, did not produce any diminution in the peripheral blood flow in any of the twenty-four subjects examined. A typical example of its effect is illustrated in Fig. 10. The intravenous injection of 0.3 mg. dihydroergocornine produced a fall in blood

pressure and heart rate, while both pulse volume and digital volume actually increased slightly. Correspondingly, the rate of blood flow, as calculated from venous congestion tests, tended to be slightly greater. The increase in pulse volume, in our opinion, was not due to active vasodilatation but can be explained by an increase in the stroke volume of the heart associated with the fall in heart rate. The actual changes in pulse volume are very well illustrated in Fig. 11.

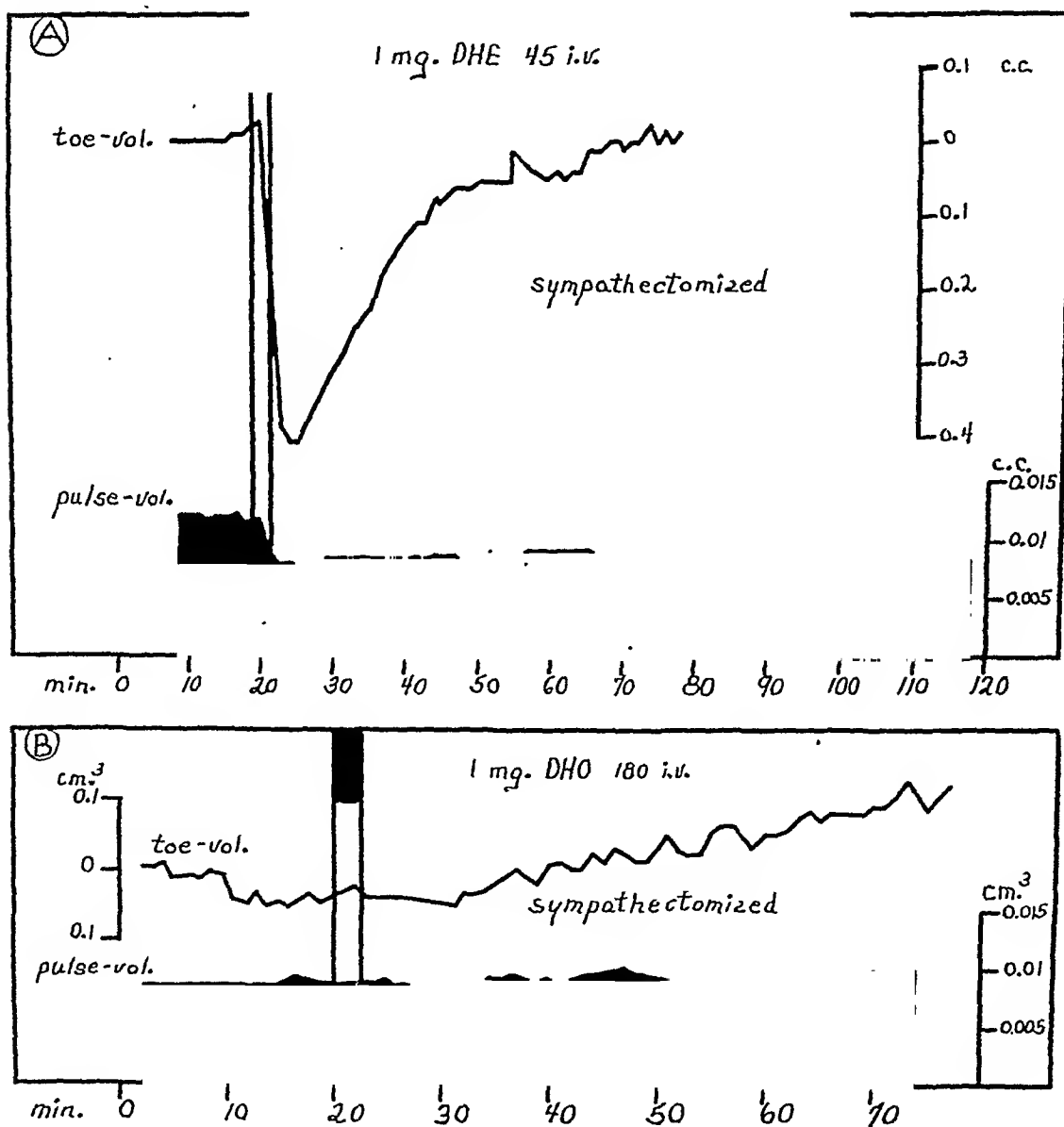


Fig. 12.— Comparison of the effect of 1.0 mg. DHE and 1.0 mg. DHO on the peripheral blood flow in a sympathectomized limb (double lumbar sympathectomy, Oct. 31, 1944, for crural ulcers). Note the marked reduction in blood flow following the injection of DHE and the absence of this constriction following the injection of DHO.

The difference in the action of the two drugs, that is, of dihydroergotamine and of dihydroergocornine, becomes very obvious when we compare the results obtained from the injection in one and the same subject (Fig. 12). The diminu-

tion, both in pulse volume and digital volume following dihydroergotamine, appears to be very pronounced when contrasted with the inertia of both following the injection of dihydroergocornine. The effects of dihydroergotamine and dihydroergocornine may also be compared by consulting Figs. 10 and 4, which were obtained in one and the same subject.

Two points emerge from these findings: first, that dihydroergocornine does not contain the principle acting directly on smooth muscle and causing peripheral vasoconstriction, but is purely vasodilator, and second, that this vasodilatation is not a direct effect on the smooth muscle but is dependent on the integrity of the sympathetic pathways. From experiments carried out by previous authors, we have to assume that we are dealing with the sympathicolytic component. Dihydroergocornine, therefore, acts purely as a sympathetic inhibitor.

Investigations concerning the effect of dihydroergocornine on the blood pressure have been reported elsewhere.⁵ The effect depends entirely upon the dose. Small doses (up to 0.5 mg.) produce a fall; larger doses, usually a rise in blood pressure. However, the relative dose varies from subject to subject, that is, 1.0 mg. may cause a fall in one and a definite rise in another patient. A smaller dose in the latter will produce a fall. The heart rate, on the other hand, consistently shows a fall, irrespective of the behavior of the blood pressure.

DISCUSSION

Dale, in 1906, first postulated that ergot alkaloids produce firstly a specific paralysis of the sympathetic motor elements which adrenaline stimulates, and secondly a stimulation of plain muscular organs. It was Rothlin^{28,29} who later could demonstrate that inhibitory, adrenergic functions of the sympathetic pathways are paralyzed as well. We have, therefore, to assume that ergot paralyzes all adrenergic function. Until recently, all available ergot preparations, except ergobasine which is purely oxytocic, contained both these ergot components. The effect of ergot alkaloids on the peripheral circulation, therefore, was inconstant and rather complex on account of the conflicting actions of the two constituents, that is, vasoconstriction and vasodilatation competing with each other. By analyzing the effect of the drugs before and after sympathectomy, we could demonstrate that the sympathicolytic action is dependent upon the integrity of the sympathetic pathways. In the sympathectomized limb, dilatation is no longer obtained and the direct pharmacologic action on plain muscular organs reveals itself in its pure form. It could be demonstrated that in the sympathectomized limb ergotamine tartrate produces a marked reduction in the peripheral blood flow, as judged by the plethysmogram. Our results, therefore, confirm those already reported in human subjects by various other authors, except, perhaps, that our results in contrast to the earlier investigations⁴² have been quantitative as well as qualitative. Graham and Wolff¹⁵ have demonstrated that the effect of ergotamine tartrate in cases of migraine results from the vasoconstrictor action of the drug on the cranial arteries. They found that the skin temperature changes with small doses only, that the pulse rate

declines by about 18 per cent, and that there is a rise in blood pressure of about 20 per cent. Their results confirm those of Pool and co-workers,²⁷ von Storch and Meritt,⁴³ and Lev and Hamburger.²⁴

It was the possibility of eliminating the direct pharmacologic action on smooth muscle of ergotamine and of producing a drug with a purely sympatholytic effect which led Stoll and Rothlin to develop new ergot derivatives. Rothlin^{30,31} and Rothlin and Bruegger³³ could demonstrate in animal experiments that hydrogenation of the ergot alkaloids produces this increase in sympatholytic effect, and at the same time, reduces the action on smooth muscle. The few clinical results so far available as to the effect of the hydrogenated ergot derivative, dihydroergotamine, seem to confirm this. Hartman¹⁶ gave the drug to twenty patients intramuscularly and found no demonstrable effect on the pulse rate, the blood pressure, the pulsations in the radial, the dorsalis pedis, and posterior tibial arteries, or in the color and temperature of the skin of the extremities. Exactly the same results were reported by Horton and associates.¹⁷ Imfeld,¹⁸ on the other hand, speaks of vasodilatation in cases of Raynaud's phenomenon, intermittent claudication, thromboangiitis obliterans, angina pectoris, and acrocyanosis. However, the circulation in most of his cases was evaluated by the clinical picture only. His dose was 1.0 to 2.0 mg. subcutaneously and 1.0 mg. intravenously; he observed a fall in blood pressure in one person, no effect in two, and a rise in four of his subjects. Rothlin,³⁰ Stoll,³⁶ Bruegger,⁶ Rothlin and Bruegger,³³ Imfeld,¹⁸ and Spühler³⁵ all hold that dihydroergotamine has hardly any, or even no effect whatsoever, on smooth muscle. The effect on the peripheral circulation in man has, however, never been critically analyzed with sensitive, quantitative methods. Using the Goetz plethysmographic method, we demonstrated that dihydroergotamine, like its original compound, ergotamine, will diminish the peripheral blood flow in the sympathectomized limb. It is, therefore, certain that dihydroergotamine still contains the direct pharmacologic action on smooth muscle and is not a purely sympatholytic drug. However, vasoconstriction from dihydroergotamine is less pronounced and apparently less lasting than from the original compound, ergotamine tartrate. We know from the experiments of Graham and Wolff¹⁵ that the effect of ergotamine is due to the vasoconstrictor action of the drug on the cerebral vessels. Spühler³⁵ has pointed out that dihydroergotamine is a very powerful drug in relieving migrainous headache, and it may be that it is the vasoconstrictor component still present in dihydroergotamine which is responsible for this beneficial effect. In contrast, in none of our patients did dihydroergocornine reduce the blood flow in the sympathectomized limb and in the normally innervated limb, the only reaction so far recorded has been vasodilatation. Dihydroergocornine, therefore, does not contain the direct action on the blood vessels so characteristic of the other ergot alkaloids and its action is purely sympatholytic.

Although our results concerning the effect of dihydroergotamine on smooth muscle do not substantiate the clinical observations of the various workers, they are supported by experiments in dogs reported by Horton and associates.¹⁷

These authors found that in the dog dihydroergotamine is a vasoconstricting agent similar to ergotamine tartrate, but that the effects of dihydroergotamine are of shorter duration than those of the latter ergot preparation. They write that additional observations on man tended to confirm this. Our results definitely prove that in man the action of dihydroergotamine is still characterized by the two active principles found in the original alkaloid, ergotamine tartrate. Dihydroergocornine, on the other hand, is the only drug which has a purely sympathicolytic effect.

The sympathicolytic effect finds further expression in the plethysmogram; it has been demonstrated by numerous authors that the plethysmogram of the normal individual does not present a straight line but shows marked spontaneous fluctuations, vasoconstriction alternating with vasodilatation. These fluctuations are generally accepted as the result of impulses which are transmitted from the vasomotor centers to the blood vessels. As Goetz¹³ has demonstrated, they are dependent on the integrity of the sympathetic nervous system and they reflect the rhythmic nature of central sympathetic vasomotor activity. Following sympathectomy, these fluctuations are no longer recorded.¹³ The effect of ergot derivatives on these spontaneous fluctuations of the plethysmogram was first investigated in Basle* with the plethysmographic method of Rothlin and Bluntschli.³² It was then demonstrated that following 1.0 mg. of dihydroergotamine or ergotamine tartrate the spontaneous fluctuations in the plethysmogram may entirely disappear. During the present investigations a similar disappearance of the spontaneous fluctuations has often been observed in normally innervated limbs following the injection of dihydroergocornine. This may be claimed as evidence that there is, to say the least, interruption of conduction of sympathetic impulses and possibly paralysis of central vasomotor activity. The disappearance of the spontaneous fluctuations in the plethysmogram following sympathectomy and following the administration of the sympathicolytic component of ergot led us to investigate the action of these sympathicolytic derivatives.

Dale ascribed the action of the component which produced "specific paralysis of the motor elements in the structures associated with sympathetic innervation" in his drugs to paralysis "of the sympathetic motor myoneural junctions in the arterial walls." We could demonstrate that in the normally innervated limb the sympathetic inhibitory (vasodilator) effect of ergotamine tartrate and dihydroergotamine is opposed by the direct-acting vasoconstrictor principle, and the effect on the peripheral circulation, therefore, is characterized by the interaction of both these principles, vasodilatation competing with vasoconstriction. In the sympathectomized extremity, however, the effect of both drugs is invariably marked vasoconstriction. The fact that the vasodilator component of ergotamine tartrate and dihydroergotamine seen in the normally innervated limb is abolished by preganglionic sympathectomy suggests, but does not prove, that its action is not on the sympathetic myoneural junction but that the sympathicolytic effect is dependent on the integrity of the sympathetic path-

*Unpublished data.

ways and that the sympathicolytic principle acts over higher nervous mechanisms. There is no reason to assume that there is a different mechanism in the case of the sympathicolytic effect of dihydroergocornine. Investigations concerning blood pressure changes after dihydroergocornine in cases of high transverse spinal lesions and following splanchnicectomy led us,⁵ in fact, to place the site of action in the medulla and/or hypothalamus.

This, to our knowledge, is the first time that it has been demonstrated that an ergot derivative acts in a purely sympathicolytic fashion in man. The possibility of therapeutic application in cases of pathologic spasm, such as Raynaud's phenomenon, acrocyanosis, and similar vascular disorders or in organic vascular diseases with superadded spasm such as embolism or in some cases of thromboangiitis obliterans, suggests itself and will be the subject of further investigations. The sympathicolytic effect of the drug has already been tested in cases of hypertension, where hyperactivity of the sympathetic nervous system has been blamed by many authors as at least a factor in maintaining the elevated arterial blood pressure. The results obtained in cases of hypertension have been reported elsewhere⁵ and indeed, in all cases of essential hypertension, dihydroergocornine caused a fall in blood pressure which in some was extremely prolonged.

SUMMARY AND CONCLUSIONS

The effect of two new hydrogenated derivatives of ergot (dihydroergotamine, referred to as DHE 45, and dihydroergocornine, referred to as DHO 180) on the cardiovascular system was investigated in twenty-four subjects and their action compared with that of ergotamine tartrate (Gynergen), with particular reference to their respective sympathicolytic properties.

It could be demonstrated, by using an accurate, quantitative method, that both ergotamine tartrate and dihydroergotamine contain the two components of ergot originally described by Dale, that is, the direct (constrictor) action on plain muscular organs and the sympathetic inhibitory (vasodilator) principle. Their effect in the normally innervated limb, therefore, is complex, due to the interaction of these two opposing elements which, however, could be separated by investigating the effect of the drugs in cases who had undergone preganglionic sympathectomy. It could be demonstrated that following sympathectomy the sympathicolytic effect (vasodilatation) can no longer be registered and that in the sympathectomized limb both ergotamine tartrate and its dihydrogenated derivative are pure vasoconstrictors. The sympathicolytic component, therefore, is dependent on the integrity of the sympathetic pathways, and dihydroergotamine is not a derivative of ergot with a purely sympathicolytic action, as has been reported by various authors.

Dihydroergocornine, in contrast, does not produce any constriction in the sympathectomized limb, and since it produces dilatation in the normally innervated limb, it has to be regarded as the first known ergot derivative which acts in a purely sympathicolytic fashion in man. The fact that the sympathicolytic principle is dependent on the integrity of the sympathetic pathways suggests

that it does not act peripherally on the sympathetic myoneural junction but over higher sympathetic centers.

Mention is made of evidence presented elsewhere that the site of action of the sympathicolytic principle of dihydroergocornine has, in fact, to be looked for in the medulla and/or hypothalamus.

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TERMINAL ELECTROCARDIOGRAPHIC PATTERNS IN EXPERIMENTAL ANOXIA, CORONARY OCCLUSION, AND HEMORRHAGIC SHOCK

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IN RECENT years, many experiments in this laboratory have provided electrocardiographic and other observations which furnish data upon the alterations in activity in mammalian hearts approaching death. Clinical papers reviewed in the concurrently published paper by Stroud and Feil¹⁶ have described the alterations of activity in dying human hearts. The fortuitous, naturally occurring changes in conditions within the organism leading to cessation of cardiac activity in human cases are not as well known to the observer as are the planned changes in the condition of the animal in well-controlled experiments. An analysis of the experimental observations may aid in discovering patterns in cardiac activity in the final stages which will contribute to better interpretation of events observed in human hearts.

The changes in the physiologic activity which are of major interest and importance in dying hearts of experimental animals are those which are observed during the time when effective pumping action is ceasing in cases of gradual cessation, or during the development of ventricular fibrillation in cases that cease suddenly via fibrillation. Changes that occur after the heart has ceased to eject blood and maintain a peripheral blood pressure do not contribute to the death of the organism. In a tabulation and discussion of modes or patterns of cardiac death, therefore, care should be taken to exclude observations which would lead to false conclusions. For example, some hearts that have stopped due to pacemaker failure or conduction failure develop a sluggish ventricular fibrillation after a period of many seconds of standstill or after extreme slowing with only an occasional ineffectual beat and with the blood pressure near zero. Such a case is not a fibrillation death, but a death from failure of the pacemaker or of the conduction system, together with weakening of the cardiac muscular contractions.

Some of the observations to be reported were compiled from the records of experiments which were performed by several investigators in our laboratory^{7,9,12} for the study of cardiac and circulation problems other than the cardiac

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approach to death. Other experiments were planned for specific quantitative study of phenomena associated with cardiac failure, especially in relation to ventricular fibrillation.^{5,6,10,19}

PROCEDURES

Dogs were used in all experiments. They were anesthetized with sodium barbital, some having preanesthetic doses of morphine.

The anoxia experiments were of two kinds: (1) with opened chests and artificial respiration; and (2) with unopened chests and natural respiration. The experiments with opened chests were performed for the primary purpose of studying the effects of anoxia upon myocardial action potentials as recorded from local contiguous bipolar leads.⁷ Observations upon the terminal changes in electrocardiograms were of secondary concern at the time, but these experiments now afford an opportunity to compare the results of anoxia combined with major surgical trauma with the effects of anoxia with little surgery. Furthermore, the animals with opened chests were unable to change the ventilation rate as anoxia developed. The artificial respiration was adjusted before rebreathing was begun to provide just sufficient overventilation to prevent any spontaneous respiratory movements while being ventilated with air with normal oxygen content. Some hyperpneic movements developed as the oxygen content of inspired air was lowered. The animals with unopened chests developed considerable hyperpnea.

Respiratory apparatus for the experiments with opened chests consisted of a large respirometer tank with an external circuit including a soda lime cartridge. The air was circulated and forced into the dogs' lungs intermittently by a piston pump. By recirculation and rebreathing the air, its oxygen content was gradually reduced. The apparatus has been illustrated and described in detail elsewhere.⁷

In the experiments with unopened chests, the animals rebreathed air from the large recording respirometer of Burlage and Wiggers, which was described recently by Randall.¹² In both kinds of anoxia experiments the percentage of oxygen in the tank could be determined, approximately, from a scale on the apparatus. Exact checks were made frequently by analyzing air samples with the Henderson-Orsat apparatus.

The coronary occlusion experiments were performed as described by Harris and Guevara Rojas.⁶ In all experiments to be included in this presentation the anterior descending artery was clamped.

The production of hemorrhagic shock was accomplished by a standardized technique developed by Wiggers and Werle.²⁰ This consists of carefully graded and timed stages of hemorrhagic hypotension as follows: ninety minutes with mean arterial pressure kept at approximately 50 mm. Hg, and forty-five minutes at about 30 mm. of mercury. These levels are produced and maintained by repeatedly drawing the amounts of blood that are required. At the end of the prescribed hypotension periods all of the withdrawn blood is reinfused. After recovery of the control arterial pressure level, the pressure again typically goes into decline and the animal dies in shock in about five to seven hours after the reinfusion. This paper describes the cardiac behavior in the last stages of pumping. Earlier electrocardiographic changes in hemorrhagic shock have been described elsewhere.⁹

RESULTS

Anoxic Anoxia.—The final changes leading to cessation of pumping in hearts exposed to gradually lowered oxygen tensions exhibit several different patterns, all of which are due to failure of the pacemaker or of conduction, or both.

In Animals with Closed Chests: The series of illustrative records to follow were taken from experiments in which the chests of the animals were left intact. Fig. 1 is a record from an animal that had been subjected to a reduced oxygen tension for almost six hours. The reduction was slow. During the first forty minutes of rebreathing, the oxygen content of the tank was dropped to 10 per cent. During the next one and one-half hours it was slowly decreased to 8.8 per cent, after which it was kept near 8 per cent for about two additional hours. After this there was a slow decline until failure occurred. The final analysis showed an oxygen concentration of 5 per cent.

The record presents a case of total heart block, the P waves and QRS-T complexes showing complete dissociation at this stage. The vagus nerves had been sectioned earlier in the experiment. Therefore, the conduction failure manifest must be regarded as an intrinsic failure of function in the specialized A-V conducting tissue. This failure occurred when the mean arterial pressure had dropped to about 25 mm. of mercury. Respiration had stopped a few seconds before the block occurred. During the latter part of the period of hypotension leading to block, there had been gradual slowing of the cardiac rate and lengthening of the P-R interval from the original 0.10 second to 0.22 second after which dissociation occurred.

Fig. 2 is from another animal in the terminal stage of a long severe anoxia. It shows failure of A-V conduction with the ventricles remaining in standstill. In Fig. 2, *A* may be seen the stage just preceding the A-V conduction failure. At this point the P-R interval had increased from the control duration of 0.10 second to about 0.25 second.

Fig. 2, *B*, taken a short time afterward, shows that only the auricles are continuing to beat. It may be inferred that in this case anoxic depression of the A-V node and other possible ventricular pacemakers prevented the establishment of an idioventricular rhythm. At the time that the long P-R intervals and conduction failure were recorded, this animal had been in severe anoxia (below 7 per cent) for more than three hours. It is unusual that an animal will live so long at this level. Ordinarily in our experiments about 8 per cent was the limit for survival for periods extending into hours.

Fig. 3 shows another pattern of cardiac approach to cessation in milder anoxia of longer duration. In Fig. 3, *A* the pacemaker suddenly ceased to discharge. Fig. 3, *B* shows the very slow ventricular rhythm which was established for a short time. Just before the pacemaker stopped the rate was 125 per minute which is quite normal for anesthetized dogs, though in this case it represented a relatively great slowing from the rate of 200 to 225 which had prevailed for the last several hours of this twelve-hour experiment. At the time the pacemaker ceased discharging there was no evidence of deterioration of A-V conduction.

The oxygen concentration in the tank at the end was 9.4 per cent. It had not been below this level at any time. Tolerance to a lack of oxygen varies appreciably in different dogs.

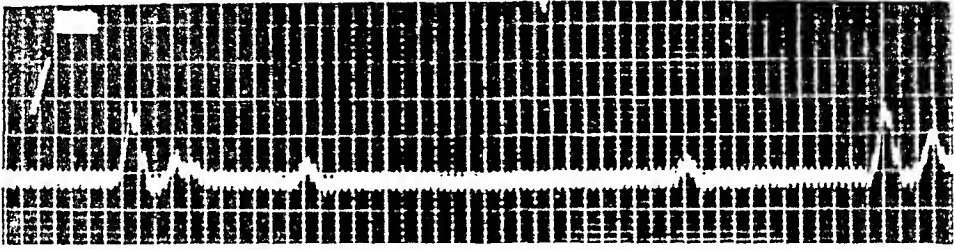


Fig. 1.—Lead III of an electrocardiogram showing complete heart block in a dog with heart failing in severe anoxia. Note abnormal width of QRS, signifying impairment of intraventricular conduction.

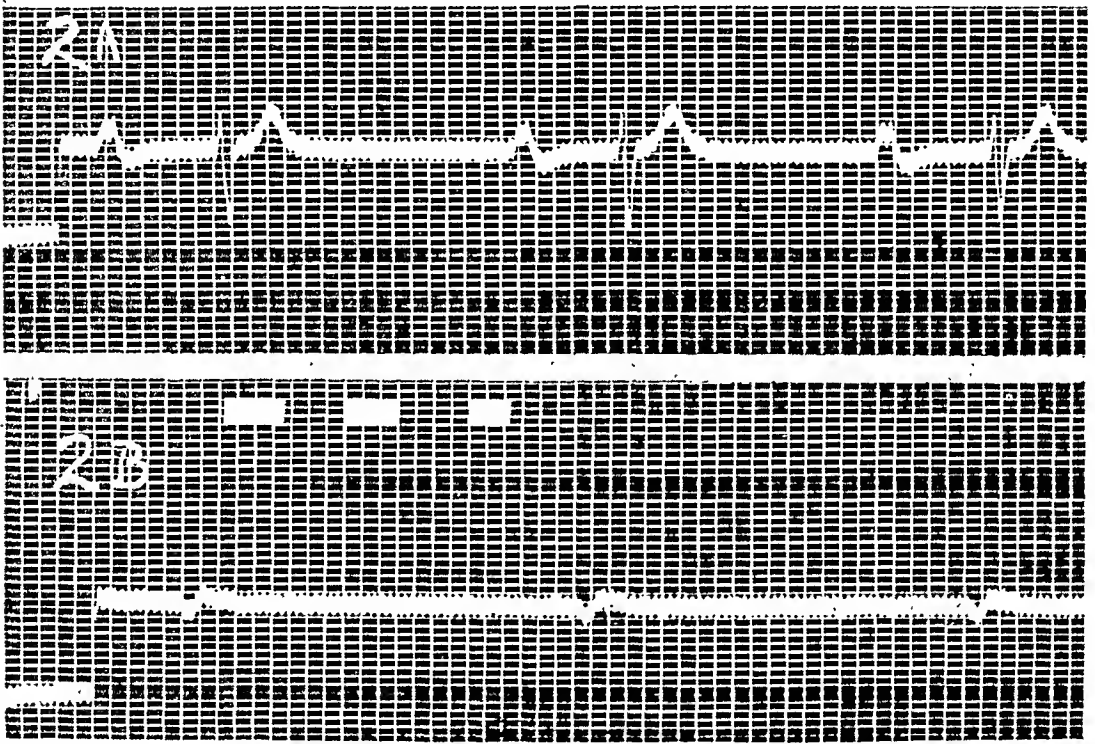


Fig. 2.—Failure of A-V conduction with ventricular standstill, the auricles continuing to beat, in an anoxic dog. A shows greatly prolonged P-R intervals, B, taken a few seconds later, contains P waves only.

Fig. 4 is from an anoxia experiment in which cardiac action was brought to an end via gradual pacemaker slowing and stoppage, followed by a period of A-V nodal rhythm. This experiment lasted more than six hours. The record is from the third and last period of rebreathing to deep anoxia in this experiment. During the greater part of the experiment and during the last rebreathing trial until five minutes prior to the time that the record shown in Fig. 4, A was made, the heart rate varied between 150 and 170 per minute. During that last preceding five

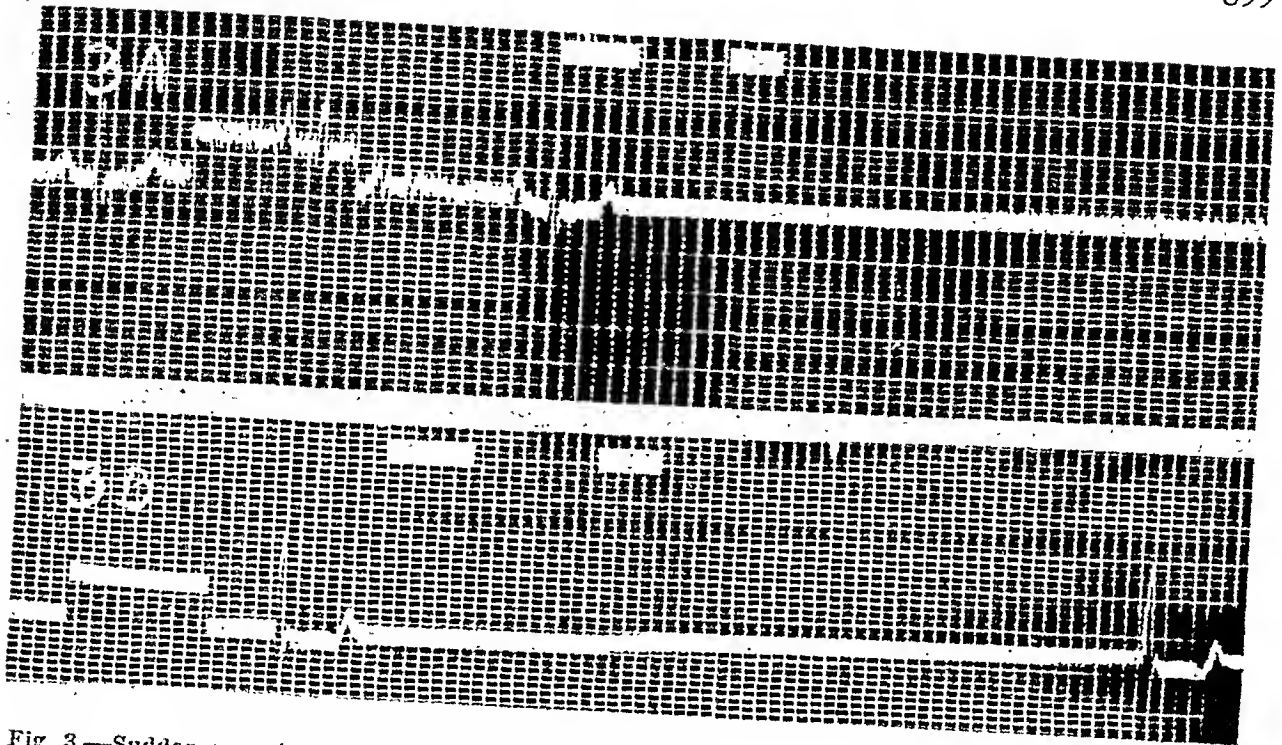


Fig. 3.—Sudden cessation of the pacemaker and development of slow idioventricular rhythm in heart of an anoxic dog. B was taken very quickly after A.

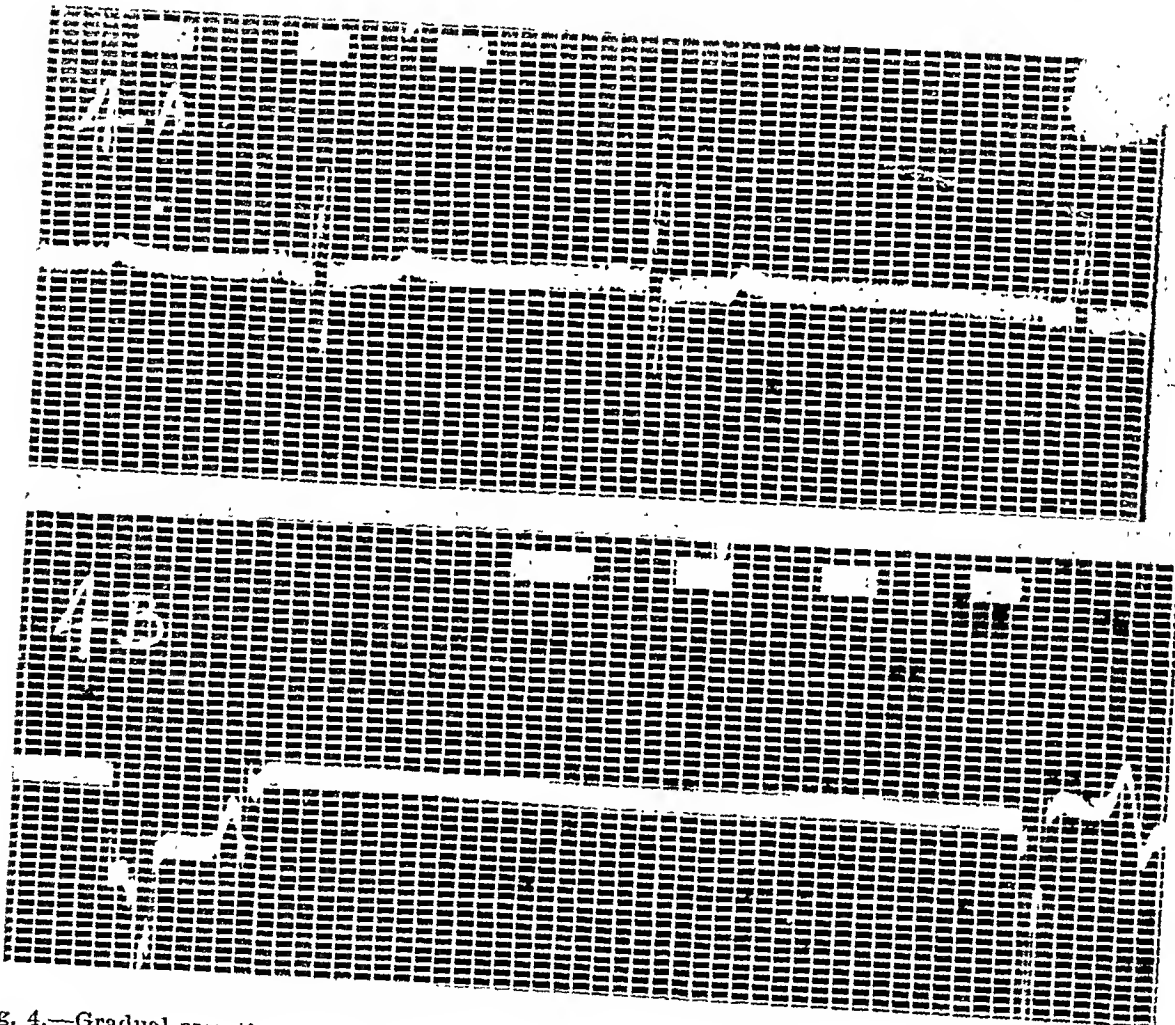


Fig. 4.—Gradual cessation of pacemaker followed by ventricular rhythm in an anoxic dog. B follows quickly after A.

minutes the rate fell to that shown in the record (about 40), and the auricles stopped very soon thereafter. The P-R intervals were normal (0.09 second) until the pacemaker stopped. Fig. 4, B shows the slow A-V nodal rhythm which followed for a minute or two before the ventricles stopped.

Of twelve animals with unopened chests which died after periods of slowly developing anoxia, independent rhythms of auricles and ventricles developed before the end in three, ventricular standstill with auricular continuation in one, very slow pacemaker and long P-R (end not recorded) in one, pacemaker failure with subsequent A-V nodal rhythm in six, and ventricular fibrillation in one.

Summarizing, there were four cases of conduction failure, six cases of pacemaker failure, one case in which conduction and the pacemaker were failing simultaneously, and one questionable case of ventricular fibrillation.

In Animals With Open Chests: In the experiments with exposed hearts and artificial respiration, the patterns of terminal activity were very similar to those already described. These changes in seven consecutive experiments as read from electrocardiograms are summarized in Table I.

TABLE I. TERMINAL CARDIAC CHANGES IN ANOXIA IN ANIMALS WITH OPEN CHESTS AND ARTIFICIAL RESPIRATION

EXP. NO.	SEQUENCE OF TERMINAL CHANGES
1	Great slowing simultaneously with long P-R; standstill, no nodal rhythm
2	Slow pacemaker and long P-R; end not recorded
3	Same as 1
4	Slight slowing with normal P-R; pacemaker stopped; nodal rhythm; complete standstill
5	Same as 2
6	Extreme slowing with normal P-R; pacemaker stopped; no nodal rhythm
7	Slowing; normal P-R; pacemaker failure; nodal rhythm

Four of these seven experiments (Numbers 1, 2, 3, and 5) exhibited simultaneous deterioration of function of the pacemaker and the conduction system. In the other three, the pacemaker failed while there was as yet no evidence of conduction deficit. These results may be regarded as identical with those from animals with unopened chests and natural respiration:

The termination of pumping activity has now been observed in more than sixty hearts dying in anoxia. Electrocardiograms have not been made in all animals with open chests, but the hearts of these animals have been observed visually. Of this large number, only one stopped in ventricular fibrillation. Many have developed sluggish fibrillary movements after an interval of total standstill following pacemaker stoppage or ventricular standstill signifying conduction failure. Considering all of the evidence from anoxic animals with opened and unopened chests, there appears to be no sound basis upon which to predict that in generalized anoxia the pacemaker will fail before conduction, or vice versa. When one fails, failure of the other is near. Stoppage via ventricular fibrillation is rare in anoxic deaths. De Somer¹⁵ stated that during fatal asphyxiation the P

wave disappears first, that is, pacemaker standstill. The sequence is, therefore, similar to that seen in about one-half of our anoxia cases.

Vagal Effects in Anoxia: The question of vagal effects in anoxia has been considered. Fig. 5 was taken from an experiment showing vagal slowing and A-V conduction block. When this record was made the arterial pressure was still normal (mean 100 mm. Hg) and the ventricles appeared vigorous. As the blood pressure declined following the stage illustrated, an interesting series of further changes occurred. At about 50 mm. Hg the auricles stopped and A-V nodal rhythm supervened for a short time. The auricles returned to activity at 30 mm. and the normal excitation sequence, with slowing rate, was observed until the pacemaker failed at about 20 mm. of mercury. Then the whole heart remained in standstill. The early block, slowing, and disappearance of P were in all probability due to vagal influence, but the pacemaker stoppage at low pressure was not. This animal had been exposed to moderate anoxia (12 to 8.5 per cent oxygen) for about the first seven hours of the experiment and to room air for two hours and forty-five minutes. After that rebreathing from the tank air (then 8.7 per cent oxygen) was started again and the reduction was allowed to continue without interruption until failure occurred about twelve minutes later. The final air sample contained 6.0 per cent oxygen. The records of vagal effects, and subsequent events of failure that were described, all occurred during the last five minutes preceding standstill.

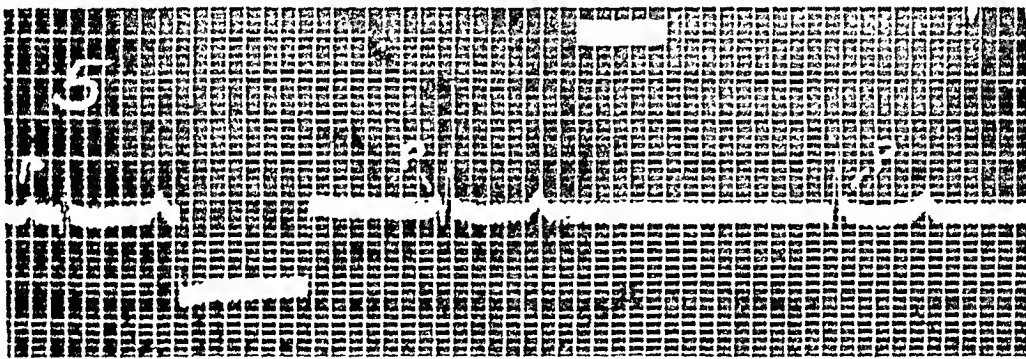


Fig. 5.—Heart block due to vagal influence in anoxic dog with well-maintained blood pressure.

In certain other experiments exhibiting slowing of the rate or block while the blood pressure was well above levels associated with failure (70 to 100 mm. Hg), the vagus nerves have been sectioned. These hearts have then resumed a rapid rate with normal pacemaker action and normal A-V conduction. Therefore, the disturbances in pacemaker function and in A-V conduction that occur in severe anoxia while the blood pressure remains high are inferred to be due to vagal impulses. However, cardiac disturbances of similar electrocardiographic appearance have been observed to occur after the blood pressure had fallen to the region of 30 mm. Hg and below, with and without intact vagus nerves. These terminal changes must be considered as due to the effects of oxygen lack in the cardiac tissues.

Long continued exposure to low oxygen concentration is not necessary to the exhibition of vagal effects. In fact, they occur much more regularly in cases of rapidly induced anoxia. In the experiments of Greene and Gilbert,³ who gave a good description of vagal effects in anoxia and differentiated between the vagal and nonvagal stages of slowing and block, the stage of complete cardiac failure was reached in about fifteen minutes. In the long continued experiment which has been described it is possible that only the last twelve minutes (when, following two hours on room air, the concentration was rapidly reduced to 6.0 per cent) have an important relation to the vagal effects. Experiments with intact vagi in which the initial slow rebreathing was carried to a more severe level (about 8 per cent oxygen) and maintained at that level for periods of one to three hours have usually not exhibited pacemaker slowing or conduction disturbances with relatively well-maintained blood pressure which are considered evidences of vagal activity.

The consensus of evidence indicates that the central cells of the cardioinhibitory mechanism may be excited (directly or reflexly?) by rapidly developed oxygen lack, and are less likely to show appreciable excitation in a very gradually developed severe anoxic state.

Coronary Occlusion.—In our studies of coronary occlusion, the only route to failure of pumping which was recorded and studied was ventricular fibrillation. In those experiments the aim was to analyze the process of initiation of ventricular fibrillation as it occurs in coronary occlusion. A description of the changes in the action of the heart as they develop minute by minute in experimental coronary occlusion has been published elsewhere.⁶ It should be sufficient here to point out only the major changes in activity. In a typical experiment the closing of the clamp on the anterior descending artery is followed by the development of ventricular ectopic systoles. The ectopic beats begin within two or three minutes of occlusion as single complexes and within another minute or two change to short runs of two or three. The groups continue to grow more frequent and become longer until, in a final paroxysm, the frequency of the ectopic discharges accelerates until coordinated activity breaks down into ventricular fibrillation. The period between occlusion and fibrillation varied between one minute, twenty seconds and nine minutes. Eighty per cent of the fibrillations (twenty out of twenty-five) occurred within the first five minutes of occlusion. In trials which did not lead to fibrillation the frequency of ectopic discharges passed through a maximum at about four to five minutes and then declined, sometimes stopping entirely by the tenth minute of occlusion.

To expedite many of the later experiments, the occluding clamp was left on the artery for periods of only ten to twenty minutes if fibrillation did not occur earlier, and then removed. After a recovery period of thirty minutes the test was repeated. If fibrillation did occur the clamp was removed immediately and the ventricles were defibrillated by use of the alternating current defibrillator. Usually it was possible to defibrillate the ventricles of the same heart repeatedly. The number of repetitions that were possible during a day's experiment varied up to a maximum of seven. In some trials, ventricles which did not fibrillate during

the period of occlusion went into fibrillation upon removal of the occluding clamp. In such cases the fibrillation occurred within a period of about one minute after opening the clamp. If a period as long as one and one-half minutes passed without fibrillation there was no further danger that fibrillation would develop. Defibrillation was difficult in these coronary occlusion experiments. Often the ventricles had to be defibrillated several times after one trial because the conditions which produced fibrillation were still present and caused immediate return to fibrillation. If, upon defibrillating, the heart remained out of fibrillation for two minutes it was generally safe from spontaneous refrillation.

After the hearts had been weakened by repeated periods of occlusion, fibrillations, and defibrillations, they usually died in standstill by pacemaker failure and conduction failure, as in anoxia.

No dog's heart has been observed to recover from ventricular fibrillation spontaneously. Without the defibrillator each fibrillation would have been a fibrillation death.

The results of all of the occlusion trials are summarized in Table II. During occlusion of the anterior descending artery there were twenty-five fibrillations in fifty trials. Of the twenty-five trials with failures to fibrillate during occlusion, there were four fibrillations upon release of the clamp. There were, therefore, a total of twenty-nine fibrillations resulting from fifty occlusions and releases. Fibrillation occurred in 50 per cent of the trials if the occlusion periods alone are considered and in 58 per cent of trials if the fibrillations upon release are included also.

In experiments upon fourteen dogs, fibrillation occurred in nine during occlusion in one or more trials. Of the five hearts that did not fibrillate during occlusion, fibrillation occurred in two upon removal of the clamp. In three there were no fibrillations during occlusion or upon release. In five there were no failures to fibrillate during occlusion.

One of the animals in which fibrillation failed in all trials was very deeply anesthetized by an overdose of sodium barbital. This may possibly be a clue to the reason for absence of fibrillation in this case. If the deep anesthesia depressed irritability, thereby preventing the generation of ectopic systoles, then fibrillation would not be expected (see discussion). No reason can be offered for the failures in the other two animals in which no fibrillation occurred.

In the coronary ligation experiments of Smith¹⁴ ventricular fibrillation occurred much less often than in the results which have just been described. Upon ligation of the anterior descending artery in eleven dogs there was ventricular fibrillation in only one. There were two ventricular fibrillations in fourteen ligations of the left circumflex artery. Wood and Wolferth²¹ indicate a higher incidence of ventricular fibrillation upon occlusion of either of the main branches of the left coronary artery. It is possible that the kind of anesthesia used makes a significant difference in the tendency to ectopic ventricular systoles and fibrillation. In our experiments and in those of Wood and Wolferth, barbiturates were used. Ether anesthesia was used by Smith.

In the one monkey heart that was used there were no fibrillations during the four occlusion periods. However, fibrillation occurred upon three of the four releases. Upon the basis of only one experiment no comparison of monkey and dog hearts can be made.

TABLE II. VENTRICULAR FIBRILLATIONS AND FAILURES TO FIBRILLATE DURING OCCLUSION AND AFTER RELEASE OF THE ANTERIOR DESCENDING ARTERY

EXP. NO.	DURING OCCLUSION		RELEASE	
	FIBRILLATION	FAILURE	FIBRILLATION	FAILURE
1	0	1	1	0
2	3	2	1	1
3	2	0		
4	5	2	1	1
5	1	0		
6	2	2	0	2
7	2	0		
8	0	2	0	2
9	0	4	0	4
10	1*	0		
11	7	0		
12	0	6	1	5
13	0	5	0	5
14	2	1	0	1
Total	25	25	4	21
On a monkey	0	4	3	1

*After this fibrillation resulting from occlusion, there were repeated spontaneous fibrillations which rendered further trials impossible.

Hemorrhagic Shock.—The final phase of pumping action in the hearts of animals dying of hemorrhagic shock has been studied from electrocardiograms correlated with kymograph records of mean blood pressures.⁹ Fig. 6 is a record of terminal activity in an experiment that illustrates a frequently occurring pattern. The tracing shown in Fig. 6, A was made during the transition from normal S-A nodal rhythm to A-V nodal rhythm. It shows brief intermittent periods of failure of the S-A pacemaker with substitution of an ectopic one in the A-V node or bundle of His and recoveries for brief periods of activity of the S-A pacemaker. Such transitional shifting of pacemakers lasted for perhaps two or three minutes

(electrocardiographic records were not continuous) and then the S-A pacemaker stopped for the last time. The record shown in Fig 6, *B* was made shortly after the final cessation of the S-A pacemaker and that in Fig 6, *C*, less than one minute later. At the time that Fig. 6, *A* was recorded, the mean blood pressure was about 22 mm. Hg and falling. When Fig. 6, *C* was recorded, the pressure was near zero. In this series of nine hemorrhagic shock experiments with frequent electrocardiograms, seven cardiac deaths occurred with pacemaker stoppage and subsequent A-V nodal or idioventricular rhythm characterizing the final stage of pumping activity. The P-R intervals were normal up to the time of pacemaker failure in all cases. One experiment was terminated by ventricular fibrillation. The final record from the other animal showed a very slow rate while maintaining a normal A-V sequence. It probably stopped in pacemaker failure as did the seven others mentioned here. Blood pressure readings in the different experiments at the time of the occurrence of pacemaker failure and the beginning of nodal rhythm varied from 40 to less than 20 mm. of mercury. In six experiments, the pressure was 30 mm. or less. The one fibrillation occurred at a pressure of 20 mm. of mercury.

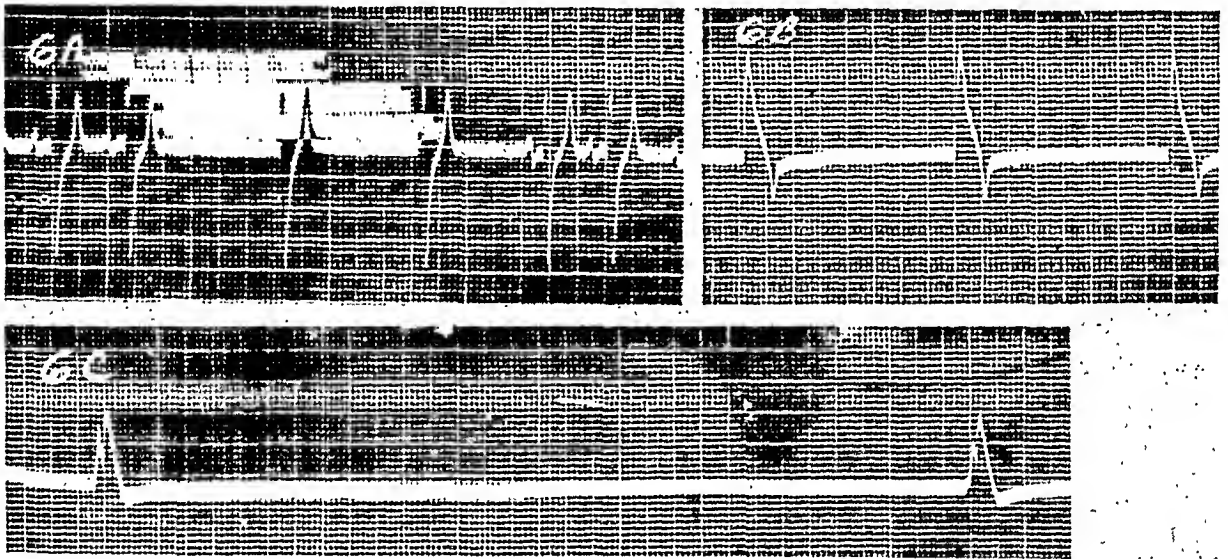


Fig. 6.—Cessation of pacemaker action, development of idioventricular rhythm, and final slowing in dog in the terminal stages of hemorrhagic shock. *A*, Intermittent periods of normal pacemaker and ventricular pacemaker rhythms. *B*, Ventricular pacemaker only. *C*, Great slowing just before standstill.

It must be borne in mind that these failures did not occur upon the mere reduction of mean arterial pressure to the region of 30 mm. of mercury. They occurred as terminal events in hemorrhagic shock. During the standard procedures to produce hemorrhagic shock earlier in each experiment, the arterial pressure was kept at about 30 mm. Hg for a period of forty-five minutes. During this time there was no evidence in any case of impending pacemaker or other cardiac failure. Hours later, upon the redecline of arterial pressure, the described changes occurred as parts of the shock syndrome.

In experiments by Negovski,¹¹ with rapid exsanguination to the point of clinical death, the terminal electrocardiograms show periods of intermittent pacemaker action and failure followed by pacemaker standstill and nodal rhythm. This sequence is identical to that seen in the terminal phase of hemorrhagic shock here. Since rapid exsanguination to 30 mm. Hg in our laboratory does not produce pacemaker failure, it is probable that in Negovski's experiments stoppage occurred after lower pressure levels were reached. Ventricular fibrillation is not mentioned in the exsanguination experiments of Negovski.

DISCUSSION

This study emphatically points out the great difference in the frequency of occurrence of ventricular fibrillation in experimental coronary occlusion as contrasted with general anoxia or hemorrhagic shock. The reasons for this difference are to be found in studies upon the nature of ventricular fibrillation^{2,18} and the changes in the activities and properties of cardiac muscle which initiate fibrillation.^{6,10}

The consensus of experimental evidence indicates that ventricular fibrillation is continuous, irregular, incoordinate, circuitous excitation and re-excitation of the various portions of the ventricular myocardium. In normally beating ventricles, circuitous re-excitation is prevented by the refractoriness of the muscle. In the dog heart the duration of the refractory period of a given small fraction of the myocardium (R-T interval of a local response) during a normal beat is about 0.18 to 0.20 second, while the period required for conduction of the excitatory process throughout the ventricular musculature (duration of QRS) is about 0.03 to 0.04 second. In a single ventricular ectopic systole induced in a normally beating heart, the period of conduction through the ventricles is about 0.05 to 0.07 second, or considerably less than one-half the duration of refractoriness. To make re-entrant excitation possible, therefore, it is necessary that the period of refractoriness be shortened markedly or that conduction be greatly slowed, or both. It has been shown¹⁰ that rapid repetitive ectopic systoles bring about both of these changes, and that if artificial stimuli are applied to the ventricles in a suitable accelerating sequence they will produce fibrillation, though the intensity of the individual shocks be but little more than the threshold for a diastolic premature systole.

Short direct current stimuli applied during the vulnerable period,^{10,19} direct current stimuli (especially anodal) of several seconds' duration,⁵ and coronary occlusion⁶ all produce ventricular fibrillation. By all of these methods the fibrillation is preceded by a repetitive and accelerating train of ectopic systoles from a discharging focus, or multiple foci in coronary occlusion. When the acceleration reaches the state that the interval between ventricular complexes of the electrocardiogram or of spikes from local leads is shortened to about 0.08 second, coordinated activity disappears and the ventricles enter the state of fibrillation.

This description of the changes that initiate fibrillation offers an explanation for the findings that a condition which produces accelerating groups of ectopic

systoles (coronary occlusion) causes fibrillation in a high percentage of trials, whereas conditions which ordinarily do not produce ectopic discharges only rarely produce fibrillation.

By multiple local leads recorded simultaneously, (it has been shown that the ectopic discharges which are characteristic of coronary occlusion arise in the boundary between ischemic and nonischemic muscle and that very high spike voltages can sometimes be recorded there)⁶ The logical interpretation is that electrochemical gradients in this zone give rise to the discharge of impulses. In overall anoxia and in hemorrhagic shock there is no such boundary. The fundamental cause of the ectopic discharges which occur for a brief period after removing the clamp from the artery to an ischemic area has not been determined. It appears possible that boundaries with electrochemical gradients exist for a fleeting moment in the neighborhood of each small blood vessel in the ischemic muscle, thus producing a vast number of potential foci.

The terminal changes that have been recorded in overall anoxia were almost equally divided between initial failure of A-V conduction and initial failure of the pacemaker. Both may be regarded as manifestations of reduction of functional ability due to oxygen lack. The rhythmic cells of the S-A node are more vulnerable to anoxia than are the A-V node and bundle in some dogs, but the opposite relation was found in others, and in some, equal susceptibilities were observed. The difference is small and probably unimportant in all cases.

Pacemaker failure was the characteristic feature of cardiac cessation in animals dying of hemorrhagic shock. Auricular stoppage and the subsequent development of A-V nodal rhythm were observed in all animals subjected to hemorrhagic shock except in the one animal in which ventricular fibrillation developed. The greater susceptibility to functional damage of the pacemaker as compared with that of A-V conduction tissues appears to be a possible difference between the reaction of the heart to slowly developing general anoxia and the reaction to hemorrhagic shock.

Studies on human cardiac death from randomly reported causes reveal patterns of terminal activity which are strikingly similar to those seen experimentally. In the cases of Hanson and associates,⁴ Sigler and co-workers,¹³ Iwasaki,⁸ and the accompanying paper of Stroud and Feil,¹⁶ the first major electrocardiographic change often was cessation of P waves. This was preceded by a gradually slowing rate. In a large proportion of cases the pacemaker failure was followed by nodal or idioventricular rhythm for a short time before ventricular standstill occurred. Auriculoventricular conduction failure with dissociation was reported in four of twenty cases of Sigler and co-workers.¹³ In one of these the terminal state resulted from a ruptured ectopic pregnancy; in two, from cerebral hemorrhage; and in one, from a bleeding gastric ulcer. Three cases of A-V dissociation were reported by Dieuaide and Davidson.¹ The authors of the latter paper stated that the terminal state probably was due to oxygen deficiency and carbon dioxide accumulation. All of their patients were victims of chronic cardiac insufficiency.

In the extensive tabulation of cases from the literature by Stroud and Feil,¹⁶ about one-third of the cases are listed as fibrillations. However, in this list the feeble terminal undulations which occur in some hearts following pacemaker failure and which do not contribute to death were counted along with the bona fide ventricular fibrillations which led to death, making the number of fibrillations listed too high. At least four of the ten listed ventricular fibrillations of Hanson and associates⁴ were of this kind, one of them being precipitated by adrenalin. Five of their apparently valid fibrillation deaths occurred in severe infectious disease and one was listed as of unknown cause. In some of the other papers, it is impossible to distinguish the real ventricular fibrillation deaths from cases with unimportant late terminal undulations. Tabulations of this kind, therefore, must be viewed with caution.

(There are reports of ventricular fibrillation in phosphorus poisoning,⁸ carbon tetrachloride poisoning,¹⁶ mercury poisoning,¹⁷ and in infectious diseases. We have no experimental counterpart for the ventricular fibrillations in poisoning and infectious disease but, in accordance with the mechanism of initiation of fibrillation discussed previously, a hyperexcitability of ventricular tissues produced by toxic agents might produce discharging ectopic foci, tachycardia, and fibrillation. Controlled studies on these subjects are needed.)

SUMMARY

Electrocardiographic records of dog hearts at the stage of termination of effective pumping in experiments upon generalized anoxia, coronary occlusion, and hemorrhagic shock have been collected and studied.

In nineteen general anoxia experiments from which terminal electrocardiograms are available, pacemaker stoppage or cessation of A-V conduction was the first gross manifestation of cardiac failure detectable in electrocardiograms in each case except one. Ventricular fibrillation occurred prior to stoppage in one. Of these nineteen animals, there were twelve with intact chests and seven with chests open for study upon the heart muscle. In a larger series of anoxic dogs with open chests and direct observation of the heart, making a total of more than sixty animals, there have been no further deaths by ventricular fibrillation, all hearts having stopped via pacemaker and conduction failure. The frequency with which pacemaker failure preceded conduction failure, and vice versa, was approximately equal in the nineteen experiments with terminal records.

In occlusion of the anterior descending coronary artery there were twenty-five fibrillations during fifty occlusion trials, and four additional fibrillations upon releases of the occluding clamp. Fibrillation occurred, therefore, in fifty per cent of the occlusions, or fifty-eight per cent of trials if fibrillations upon release are included.

In nine hemorrhagic shock experiments seven hearts failed by pacemaker stoppage, another probably did also, and one stopped via ventricular fibrillation.

The experimental conditions which produce a gradual overall diminution in the functional capacity of the cardiac tissues without predisposition to ectopic

ventricular systoles produced failure of the pacemaker or of A-V conduction, but very rarely induced ventricular fibrillation. The experimental condition (coronary occlusion) which predisposes to trains of ectopic ventricular systoles produced a high percentage of ventricular fibrillations. The reasons are discussed.

Observations in a few representative clinical papers are reviewed and compared with the experimental observations. Considerable agreement with the experimental patterns and with the conclusion stated in the preceding paragraph was found.

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THE TERMINAL ELECTROCARDIOGRAM: TWENTY-THREE CASE REPORTS AND A REVIEW OF THE LITERATURE

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THE mechanism of death in the human heart has been an interesting topic for many centuries. The ancients believed the left auricle to be the last portion to stop contracting visibly. In 1850, Hoffa and Ludwig¹⁸ showed that electrical stimulation of the mammalian heart caused ventricular fibrillation and death. In 1887, MacWilliam²⁶ predicted ventricular fibrillation to be the principal factor in sudden death. In 1912, Robinson³³ reported the first electrocardiograms taken in the agonal state. In 1915, Allbutt¹ proposed an overwhelming, sudden vagus stimulation with complete standstill as a cause of sudden death. Since then, many authorities^{4,13,17,21,41} have come to believe that ventricular fibrillation probably is the main factor in sudden death of patients with severe heart disease with angina pectoris and/or myocardial infarcts. However, Grieco and Schwartz¹⁰ have predicted recently that as many sudden deaths in coronary heart disease are caused by standstill as by sudden ventricular fibrillation. There has been a great deal of discussion as to the possible patterns in terminal electrocardiograms.

We are presenting twenty-three cases in which the electrocardiograms were obtained before and during the terminal activity of the heart. The available literature has been reviewed and will be discussed briefly in connection with our findings and the experimental data of Harris^{15b} on the electrocardiograms of dogs dying from anoxemia, from hemorrhage, and from clamping of a coronary artery.

METHOD

When practical, the electrodes were attached to the moribund patient before clinical death. The three standard leads were obtained and also a few chest leads. Tracings were taken intermittently or continuously on Lead II until the string became motionless. Several cases were obtained during operations under general anesthesia. In two cases, hearts that were "dead" clinically by electrocardiogram were revived. Both patients died some time afterward, but the original death was used without obtaining records of the "second" death. Unless otherwise stated, clinical death occurred some time before the electrocardiographic tracing became flat.

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CASE REPORTS

CASE 1.—R. W., a woman, 40 years of age. *Hypertensive cardiovascular disease with recent hemorrhage into the pons.* The patient collapsed suddenly on the street and was admitted in coma with left-sided paralysis. Bloody spinal fluid was noted. She died in one hour. Necropsy revealed recent hemorrhage into the pons with extension. The heart, weighing 490 grams, was dilated and hypertrophied. The kidneys revealed chronic pyelitis and moderate nephrosclerosis.

Electrocardiogram: Initial tracing revealed a ventricular rhythm at a rate of 115 per minute with occasional ectopic ventricular beats. Rate suddenly slowed to 59 per minute with increasing intraventricular block. The ventricles stopped suddenly while the auricles continued to beat for about thirty seconds at a rate of 45 per minute.

CASE 2.—A. F., a man, 42 years of age. *Carbon tetrachloride poisoning with uremia.* The patient was admitted with symptoms of renal failure and died on the twenty-first hospital day despite peritoneal lavage. Necropsy revealed severe acute nephrosis, necrosis of the liver, diffuse bronchopneumonia of both lungs, and a dilated heart weighing 470 grams.

Electrocardiogram: Initial tracings during hospitalization revealed right bundle branch block that disappeared temporarily during peritoneal lavage (potassium intoxication?). At death, regular sinus rhythm was followed by increasing P-R interval. Nodal rhythm supervened. Finally, a slow ventricular rhythm appeared abruptly. This merged into flutter and terminal ventricular fibrillation.

CASE 3.—P. S., a woman, 59 years of age. *Severe diabetes with recent myocardial infarction.* This patient was admitted because of a history suggestive of myocardial infarction three weeks previously and progressive dyspnea. She died suddenly on the fourteenth hospital day while in uremia. Necropsy was not performed.

Electrocardiogram: On admission, tracing revealed evidence of acute anterior infarction. Digitalization slowed the rate to 40 per minute. Wandering pacemaker was then noted. The terminal electrocardiogram revealed a gradually widening QRS. There ensued periods of prolonged cardiac standstill interrupted by bizarre ventricular complexes. This continued for about fifteen minutes until complete standstill. No P waves were seen.

CASE 4.—C. C., a woman, 37 years of age. *Hypertension, central nervous system syphilis, sicklelema, and tuberculous keratitis.* Terminal hospitalization was for weakness and nausea. Flaccid paralysis of the lower extremities and nuchal rigidity were noted. Laboratory tests revealed the nephrotic syndrome. The spinal fluid Wassermann was positive. Death occurred on the tenth day. Necropsy revealed syphilitic meningoencephalitis and myelitis; hypertrophied and dilated heart (350 grams); stellate wrinkling and retraction of the aorta; sicklelema; and bilateral pyelonephritis.

Electrocardiogram: The record showed nodal tachycardia with ectopic ventricular beats until respirations ceased. Then the ventricular rate slowed and runs of several monophasic waves interrupted by long periods of standstill appeared. Caffeine and intracardiac adrenalin did not prevent complete standstill in four minutes.

CASE 5.—C. K., a man, 74 years of age. *Prostatic carcinoma with metastases.* A transurethral resection for urinary retention was done four months prior to the terminal admission because of anasarca. Total blood proteins were 3.9 Gm. per 100 cubic centimeters. Chest x-ray revealed fluid at both bases and possible metastases. The heart size was normal, but the liver was palpable three fingerbreadths below the costal margin. He died rapidly. Necropsy was not performed.

Electrocardiogram: Previous records showed left axis deviation and sinus coupling. Terminal strips revealed a slow ventricular rate without visible P waves. These waves were bizarre and were gradually reduced in amplitude. After two minutes there was no further movement of the string.

CASE 6.—L. H., a man, 60 years of age. *Diabetes mellitus, lymphatic leucemia, hemachromatosis, and tuberculous pneumonia.* The patient was hospitalized terminally and died suddenly

on the thirty-sixth day. Necropsy revealed the additional findings of arterial nephrosclerosis, marked sclerosis of the coronary arteries, and slight myocardial fibrosis.

Electrocardiogram (Fig. 1): Previous tracings revealed sinus tachycardia with low voltage in all leads. The terminal tracing was started when respirations were two per minute and the patient pulseless. It lasted five minutes, thirty-four seconds. Sinus tachycardia with low amplitude merged into slow nodal rhythm. Standstill then occurred and was followed by slow ventricular rhythm. This was followed by ventricular flutter and terminated in coarse fibrillation.

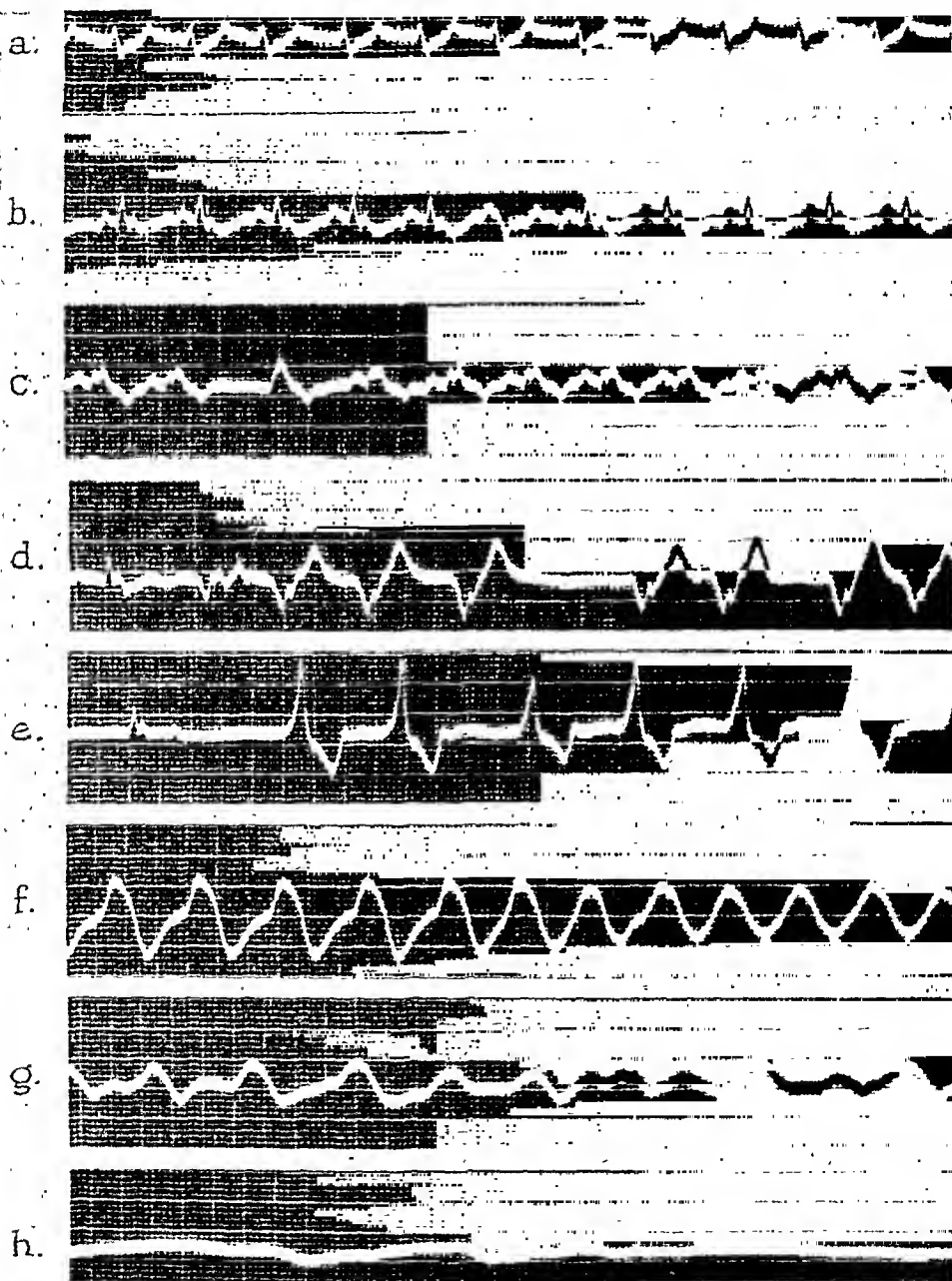


Fig. 1.—Case 6. See text for description.

CASE 7.—K. H., a woman, 55 years of age. *Diabetes mellitus, hypertension, arteriosclerotic heart disease, and recent and old myocardial infarcts.* The terminal hospitalization was due to severe angina pectoris. She was in shock and in congestive failure. She expired as the electro-

cardiographic tracing was started. Necropsy revealed marked stenosing coronary arteriosclerosis with recent and remote infarcts of the left ventricle. Diffuse arteriolar hyaline necrosis was found in the pancreas, kidneys, and adrenals.

Electrocardiogram (Fig. 2): The terminal record revealed prolonged P-R interval with intra-ventricular block, auricular standstill with slow ventricular rate, and final standstill.

CASE 8.—W. R., a man, 60 years of age. *Diverticulitis of the colon, peritonitis, and left hemiplegia*. On hospitalization, symptoms and signs suggested diverticulitis. X-ray confirmation was obtained. On the nineteenth day the patient developed peritonitis. On the next day, left hemiplegia occurred and he died suddenly while an electrocardiogram was being taken. Necropsy was not obtained.

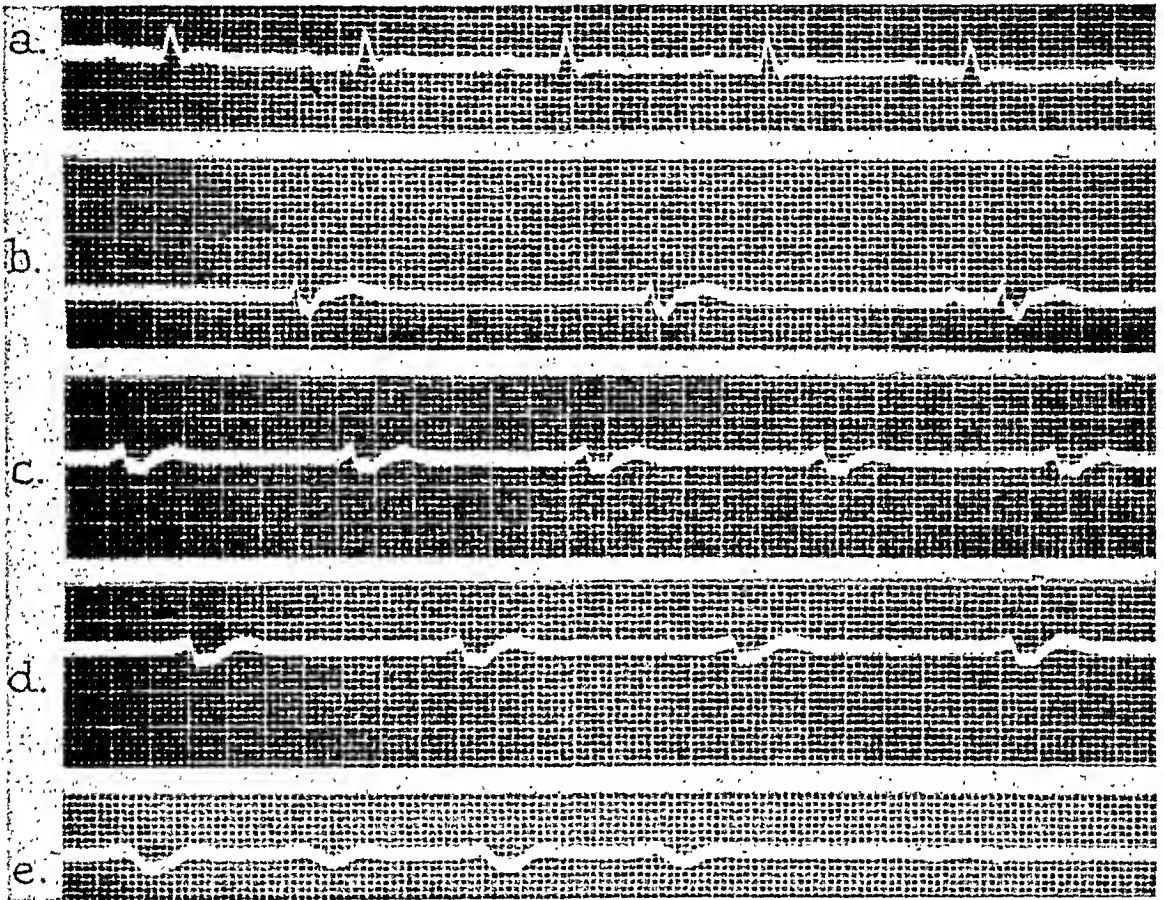


Fig. 2.—Case 7. See text for description.

Electrocardiogram: The standard leads showed sinus tachycardia and right bundle branch block. As he expired, the terminal strip revealed irregular ventricular complexes at a rate of 40 per minute with markedly elevated S-T segments. No P waves were noted. Short runs of ventricular tachycardia arising from varying foci were followed by gradual slowing and widening of the beats. Finally, periods of complete standstill alternating with short runs of bizarre ventricular complexes ended in standstill.

CASE 9.—M. K., a man, 62 years of age. *Hypertensive and arteriosclerotic heart disease with recent and old myocardial infarcts*. This patient was hospitalized for suspected acute myocardial infarction. He was in congestive heart failure. The next morning, although seemingly comfortable, he died suddenly while a tracing was being taken. Necropsy revealed marked arteriosclerosis of the left coronary artery with a recent thrombus in the anterior descending branch. Other findings were remote infarcts of the posterior portions of the left ventricle and interventricular septum, splenic infarct, and recent and remote infarcts of the right auricular appendage.

Electrocardiogram (Fig. 3): Previous records revealed auricular fibrillation with digitalis effect, and just prior to admission, sinus arrhythmia with frequent auricular and ventricular ectopic beats. The agonal strip, which was run almost continuously for forty minutes, revealed coarse ventricular fibrillation followed by auricular flutter, standstill, and a few terminal, slow, monophasic ventricular (?) complexes.

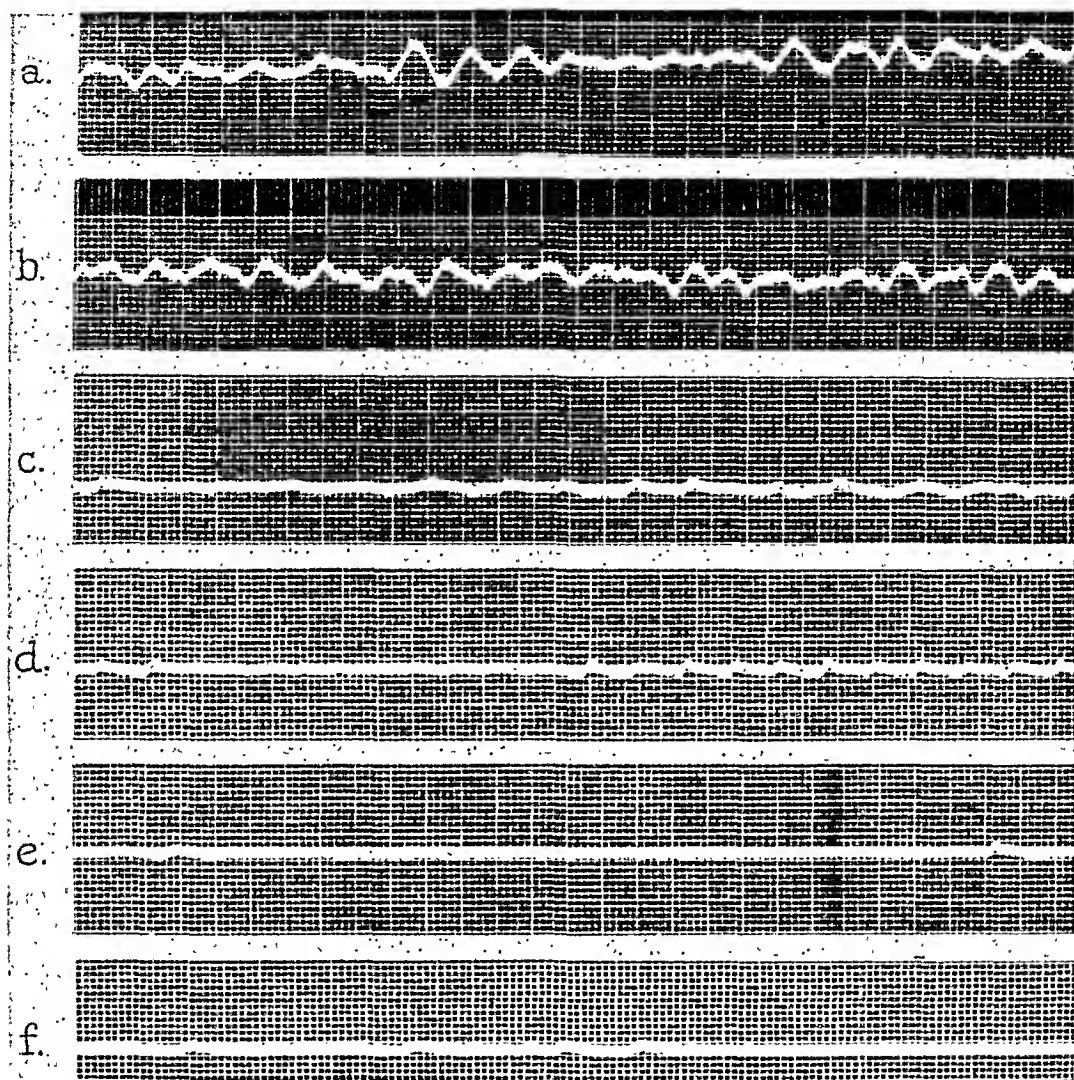


Fig. 3.—Case 9. See text for description.

CASE 10.—E. J., a boy, 10 years of age. *Comminuted fracture of right tibia with hemarthrosis and foreign body of the right knee joint.* During operation under gas-oxygen-ether anesthesia the pulse disappeared. The fibrillating ventricles were exposed and 5.0 c.c. of 5 per cent procaine were injected into the cavity of the right ventricle and the ventricles were shocked to standstill by the Wiggers technique.⁴² The heart was massaged manually. After approximately twenty minutes, effective rhythm was obtained. The heart continued to beat for seventy minutes. Necropsy revealed moderate stenosis of the right coronary artery in addition to the expected findings.

Electrocardiogram: Tracings were taken after defibrillation. They first revealed auricular fibrillation with a ventricular rate of 45 per minute, low QRS complexes and depressed S-T segments. Twenty minutes later, auricular flutter at a rate of 66 per minute with a ventricular rate

of 17 per minute was followed by auricular standstill. After the onset of the terminal rhythm, ventricular fibrillation occurred.

CASE 11.—G. C., a man, 60 years of age. *Acute myocardial infarct*. While dancing, this man was stricken with an attack of substernal oppression. He gave a history of previous anginal attacks. While one of us was taking an electrocardiogram he collapsed suddenly and died. Necropsy was not permitted.

Electrocardiogram (Fig. 4): The three standard leads revealed normal sinus rhythm at a rate of 84 per minute with rare premature ventricular beats and the typical pattern of acute posterior myocardial infarct. During shifting to the chest lead, the patient collapsed and a record started a few seconds later revealed coarse ventricular fibrillation.

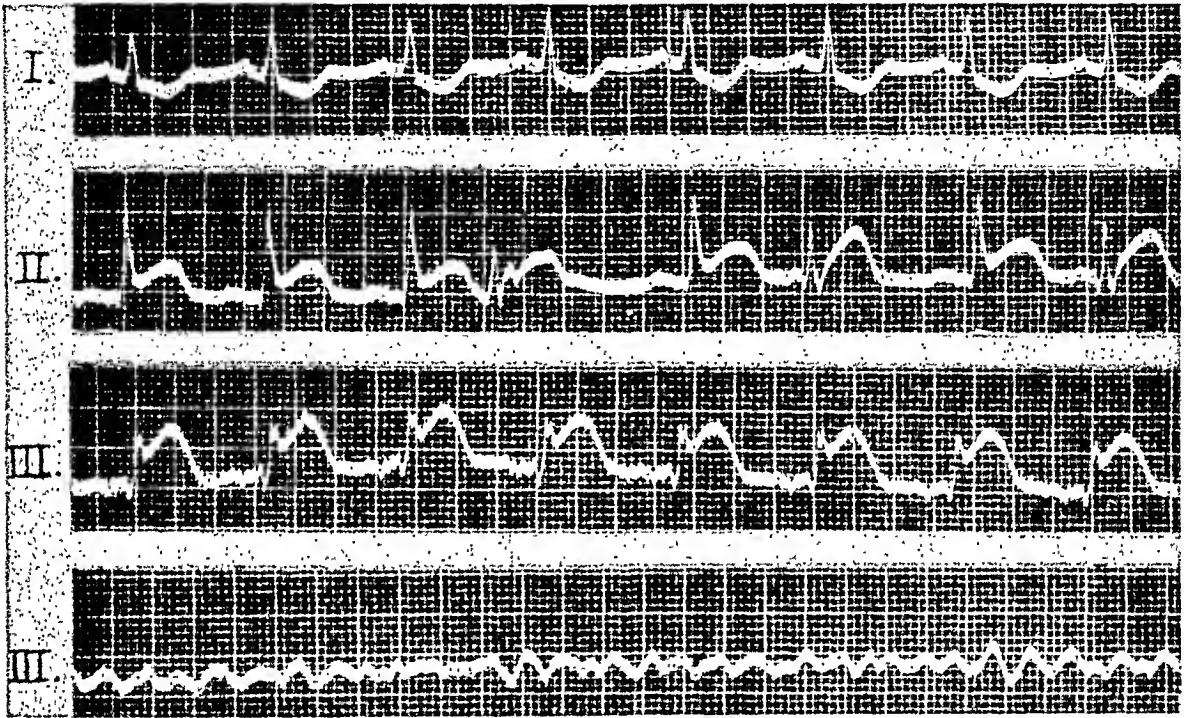


Fig. 4.—Case 11. See text for description.

CASE 12. H. G., a man, 68 years of age. *Hypertensive and arteriosclerotic heart disease*. This patient had been followed for many years and had suffered several attacks of congestive heart failure and a cerebrovascular accident. On admission he was confused and in acute congestive failure. Blood urea nitrogen was markedly elevated. Despite 1.0 mg. of Cedilanid given intravenously in divided doses, he died in eleven hours. Necropsy revealed pneumonia of both lower lobes, moderate stenosis of the aortic valve, marked generalized arteriosclerosis including the coronary and pulmonary arteries, acute fibrinous pericarditis, myocardial fibrosis, and left ventricular hypertrophy and dilatation (heart weighed 510 grams).

Electrocardiogram: The initial record revealed auricular fibrillation with a ventricular rate of 148 per minute. Following Cedilanid, nodal rhythm was noted at a rate of 70 per minute. The ventricular complexes broadened and the rhythm became irregular. The T wave, previously flat, became upright and many ectopic ventricular beats appeared. Finally, there was a sudden burst of ventricular fibrillation, with gradual decrease in amplitude, and standstill.

CASE 13.—C. G., a man, 71 years of age. *Hypertensive and arteriosclerotic heart disease; Stokes-Adams syndrome and congestive failure*. This patient was admitted for the last time in congestive failure. Despite digitalis, diuretics, and paracenteses, he died suddenly on the fourteenth hospital day after a series of attacks of cardiac standstill lasting from fifteen to forty-five seconds. Necropsy was not permitted.

Electrocardiogram: The terminal tracing showed slightly irregular, upright, monophasic QRS complexes at a rate of 84 per minute with no visible P waves. These ventricular complexes suddenly stopped, revealing notched P waves at a rate of 35 per minute. Ventricular rhythm again started after twenty seconds at the rate of 75 per minute. This lasted about ten seconds, and the terminal event was gradual slowing and flattening of the auricular waves at a rate of 22 per minute with complete ventricular standstill.

CASE 14.—M. L., a woman, 27 years of age. *Patent ductus arteriosus with subacute bacterial endocarditis due to hemolytic Staphylococcus albus.* The patient was admitted with a typical history, signs, and symptoms of both conditions. After preliminary penicillin therapy, ligation of the duct was attempted under gas-oxygen-ether anesthesia. As the pericardium was opened, the arterial pressure dropped suddenly. A generalized convulsion started on the left side, and soon after, the heart stopped. After massage, local procaine, and defibrillation, ventricular fibrillation persisted. After about six more shocks, fairly normal contractions started. After the intracardiac injection of adrenalin, the heart beat for five minutes and again stopped. Massage was successful and the ductus was ligated with disappearance of the thrill. The chest was closed and the patient began to breathe spontaneously. She died nine hours later without regaining consciousness. Necropsy revealed a ligated patent ductus arteriosus, subacute bacterial endocarditis of the pulmonary valve, recent pulmonary infarcts of the lower lobes, and what appeared to be an ante-mortem embolus in a cerebral artery on the right.

Electrocardiogram: Tracings were taken from 8:25 A.M., just before anesthesia, until the patient left the operating room. The last nine hours were not recorded. The first strip showed sinus tachycardia. This continued until just before the convulsion when ectopic ventricular beats occurred. Next there were short bursts of supraventricular beats until complete standstill occurred. This was followed by coupled ventricular beats. Then ventricular flutter merged into ventricular fibrillation. With further shock therapy the tracings reverted to ventricular tachycardia and eventually auricular fibrillation with fast ventricular rate.

CASE 15.—I. F., a man, 52 years of age. *Arteriosclerotic heart disease with remote myocardial infarction and fibrous obliteration of pericardium.* This man was admitted for pericardiectomy because of calcification of the pericardium overlying the right ventricle. He had suffered a myocardial infarct nine years previously. Recently congestive failure had occurred. Under gas-oxygen-ether anesthesia, the heart stopped beating before the mediastinum was entered. Incision of the pericardium and cardiac massage produced a feeble beat. The wound was closed and the patient died several hours later. Necropsy revealed fibrous obliteration of the pericardium over the right ventricle; coronary arteriosclerosis with remote occlusions of the circumflex and anterior descending branches of the left coronary artery, remote calcified infarct and aneurysm of the anterior half of the left ventricle and interventricular septum, and the results of the recent surgery.

Electrocardiogram: Routine tracings before operation were typical of remote anterior infarction. During operation, sinus tachycardia was supplanted by ventricular standstill. This was followed by A-V dissociation with a slow, irregular ventricular rhythm of 35 per minute, while the auricular rate was 60 per minute. About an hour later, bizarre ventricular complexes with periods of standstill occurred. Next was noted ventricular standstill followed by slow, undulating ventricular waves (50 per minute). Then irregular ventricular complexes with retrograde P waves were noted and periods of complete standstill. Finally, a few rare waves, probably of auricular origin, terminated electrical activity.

CASE 16.—M. T., a woman, 49 years of age. *Hypertensive cardiovascular disease, dissecting aortic aneurysm, and syphilis.* About an hour before admission, the patient suffered excruciating back pain and vomited. On admission, as in the past, she was in congestive heart failure. She was given morphine sulfate and died suddenly while an electrocardiogram was being taken. Necropsy was not permitted.

Electrocardiogram: Previous records revealed left axis deviation and digitalis effect. On the first of the terminal records, standard leads revealed sinus tachycardia. The final strip showed A-V dissociation with the auricles beating at a rate of 60 per minute and the ventricles at 51 per

minute. The ventricular complexes were very wide and bizarre. The ventricular rate slowed to 12 per minute and stopped. P waves disappeared when the ventricular rate was 24 per minute.

CASE 17.—V. S., a woman, 30 years of age. *Air embolism*. This healthy woman was given a Rubin test for tubal patency under nitrous oxide anesthesia. At the end of the procedure, the blood pressure was unobtainable and respirations fell to 4 per minute. Within six to ten minutes the pericardium was incised and the heart beat restored after defibrillation and massage. There was evidence of air in the veins at this time. Later the chest was reopened and a hemorrhage stopped. Patient expired nine hours later. Necropsy revealed nothing beyond the expected surgical trauma and slight salpingitis.

Electrocardiogram: Tracings were started just after the emergency operation began. The first strip revealed right bundle branch block at a rate of 150 per minute. Next ventricular fibrillation alternated with flutter at 152 per minute. (During these strips the patient was dead clinically.) The next strip showed small ventricular complexes at a rate of 75 per minute which slowed to 20 to 30 per minute, with auricular fibrillation. Next the patterns of ventricular flutter, slow ventricular rhythm, ventricular fibrillation, ventricular flutter, and a multifocal ventricular rhythm occurred in that order. Finally, ventricular tachycardia at a rate of 136 per minute changed to sinus bradycardia at 46 per minute, and the last strip revealed a sinus tachycardia at 125 per minute. Records were not taken at the second "clinical" death.

CASE 18.—M. S., a woman, 62 years of age. *Massive, confluent bronchopneumonia with congestive heart failure*. This delirious patient was admitted with pneumonia of three weeks' duration. The liver was enlarged and ankle edema was noted. She died in a few hours. Necropsy revealed massive, confluent bronchopneumonia throughout both lungs. The heart appeared normal. The liver was congested.

Electrocardiogram: Supraventricular tachycardia with frequent ventricular premature beats changed to auricular fibrillation with a ventricular rate of 88 per minute. Then broad ventricular complexes occurred at 54 per minute. Finally, ventricular tachycardia appeared (rate 163 per minute) and sudden complete standstill terminated the record.

CASE 19.—A. G., a man, 65 years of age. *Hypertension, gastrointestinal bleeding, and (?) acute myocardial infarction*. Prior to admission, this patient had substernal oppression on exertion. On admission, he stated that hematemesis and melena had been present for three days. The hemoglobin dropped during hospital stay from 9.5 Gm. to 8.0 Gm. per 100 cubic centimeters. On the third hospital day, a crushing substernal pain occurred with shock. He died in forty-five minutes while an electrocardiogram was being taken. Necropsy was refused.

Electrocardiogram: Previous records taken on his first two hospital days revealed abnormal left axis deviation. The terminal strip showed coarse ventricular fibrillation.

CASE 20.—A. W., a man, 39 years of age. *Hypertensive heart disease with recent and old myocardial infarcts*. The patient gave a history of myocardial infarct six months prior to admission and stated he "shot several pulmonary emboli." Fifteen minutes before admission he noted crushing substernal oppression. Despite medication, his symptoms increased and he expired less than an hour after admission while an electrocardiogram was being taken. Necropsy was refused.

Electrocardiogram: The initial standard and chest leads revealed sinus tachycardia with intraventricular conduction defect. This changed to nodal rhythm with dropped ventricular beats (rate 22 per minute). This changed to A-V dissociation (auricular rate 50 and ventricular rate 33 per minute). Finally, after a brief period of nodal rhythm (rate 28 per minute), the P waves disappeared and there were bizarre ventricular complexes at a rate of 10 per minute. Cardiac standstill then terminated the record.

CASE 21.—A. C. S., a man, 75 years of age. *Benign prostatic hypertrophy and angina pectoris (?)*. The patient was admitted because of urinary retention. He gave a history suggestive of anginal syndrome. Physical examination revealed no cardiovascular abnormalities except peripheral arteriosclerosis. The heart was within normal limits by x-ray examination. The first stage prostatectomy was uneventful. During the second stage, under open-drop-ether anesthesia, the

heart rate quickened and the blood pressure rose rapidly. Pulmonary edema ensued. Following intravenous administration of Cedilanid, 1.6 mg., and aminophylline, the patient expired within an hour. Necropsy was not obtained.

Electrocardiogram: The initial tracing upon admission showed bradycardia and left axis deviation. The terminal strip, started about fifteen minutes before clinical death, revealed sinus tachycardia (rate 188 per minute) which shifted suddenly to ventricular tachycardia (rate 172 per minute). Later ventricular fibrillation occurred. The next strip showed small fibrillatory waves for about two seconds. Standstill followed for another few seconds. Then there appeared some irregularly spaced, bizarre ventricular complexes at a rate of 5 to 10 per minute which lasted several minutes and were followed terminally by a fine ventricular fibrillation that lasted six seconds.

CASE 22.—W. H., a man, 50 years of age. *Hypertensive cardiovascular disease with recent and old infarcts of lungs and heart.* He had been digitalized for congestive heart failure but had taken no digitalis in the month prior to hospitalization. He was admitted with hemoptysis. He received 1.4 Gm. of digitalis by vein and muscle in the eighteen hours prior to death. While an electrocardiogram was being taken, he died suddenly. Necropsy findings consisted of a dilated heart weighing 940 grams with recent infarction of the right auricle, old healed infarction of the apex of the left ventricle and interventricular septum, and old and recent infarcts of the lungs. There was marked, generalized, severe arterial and arteriolar sclerosis.

Electrocardiogram: Previous tracing revealed left bundle branch block. Terminal strip revealed supraventricular tachycardia (rate 150 per minute) with prolonged QRS and terminal ventricular fibrillation.

CASE 23.—J. M., a man, 87 years of age. *Arteriosclerotic heart disease with Stokes-Adams syndrome and aortic stenosis.* (The record of this patient was taken by Dr. Austin Weisberger who kindly gave us permission to include it in this study.) This aged man was admitted to a Naval Hospital because of frequent bouts of fainting. He was not in congestive failure. Treatment with ephedrine sulfate was ineffective. His terminal attack ended in anoxic convulsions. The heart continued beating at least two hours after respirations ceased. At necropsy the findings were marked, generalized arteriosclerosis, stenosis of the aortic valve, and a hypertrophied heart.

Electrocardiogram: Tracing taken two months prior showed sinus bradycardia with a rate of 56 per minute. Tracing about one week prior to death revealed ventricular standstill upon carotid sinus pressure. The record several days prior to death showed dissociation with an auricular rate of 62 and a ventricular rate of 32 per minute. The terminal tracing started with frequent episodes of ventricular asystole. Bizarre ventricular complexes ensued at a slow rate. The rate increased to 120 per minute and then slowed. In the meantime, the auricles beat independently at about 70 per minute. Finally, there was sudden complete ventricular asystole. The auricular rate slowed to 30 per minute and stopped for five seconds. This was succeeded by irregular, wide, ventricular waves at a rate of 70 per minute with inverted T waves. Then, regular small ventricular complexes with deep Q and upright T waves occurred. Then followed ventricular flutter at a rate of 70 per minute lasting twenty seconds. These waves became irregular, smaller, and ceased gradually.

SUMMARY OF OUR CASES

Our twenty-three patients ranged in age from 10 to 87 years. No definite heart disease could be found in seven cases (Table I). Of these latter patients, in one case, sudden death was due to ventricular fibrillation, while in three, ventricular fibrillation was but the terminal phase occurring long after "clinical" death. The remaining three patients of this group showed no ventricular fibrillation. The heart slowed and then stopped abruptly. Of the sixteen cases of obvious heart disease, seven ended with ventricular fibrillation (Table II). Of

TABLE I. DEATHS NOT DUE TO HEART DISEASE

PATIENT	SEX	AGE	NECROPSY	DIAGNOSIS	TERMINAL ECG PATTERNS
2. A. F.	♂	42	Yes	Carbon tetrachloride poisoning, uremia	Ventricular slowing and fibrillation
5. C. K.	♂	74	No	Transurethral resection	Ventricular slowing and standstill
6. L. H.	♂	60	Yes	Leucemia, tuberculosis	Ventricular slowing and fibrillation
8. W. R.	♂	60	No	Peritonitis, hemiplegia	Ventricular slowing and fibrillation
10. E. J.	♂	10	No	Fractured left tibia, foreign body	Ventricular fibrillation (sudden)
17. V. S.	♀	30	Yes	Air embolism	Ventricular fibrillation and flutter
18. M. S.	♀	65	Yes	Massive bronchopneumonia	Ventricular tachycardia and sudden standstill

Summary: Seven cases, four ventricular fibrillation

TABLE II. DEATHS DUE TO HEART DISEASE

PATIENT	SEX	AGE	NECROPSY	DIAGNOSIS	TERMINAL ECG PATTERNS
1. R. W.	♀	40	Yes	Hypertension, cerebral hemorrhage	Ventricular slowing and standstill; auricles 30" longer
3. P. S.	♀	59	No	Diabetes, myocardial infarct	Ventricular slowing and standstill
4. C. C.	♀	37	No	Hypertension, CNS syphilis, sickleemia	Ventricular slowing and standstill
7. K. H.	♀	55	Yes	Hypertension and arteriosclerosis, diabetes, old and recent infarct	Ventricular slowing and standstill
9. M. K.	♀	62	Yes	Hypertension and arteriosclerosis, recent and old infarct	Sudden ventricular fibrillation (standstill and slow ventricular rate)
11. G. C.	♂	60	No	Myocardial infarct	Sudden ventricular fibrillation
12. H. G.	♂	68	Yes	Pneumonia, hypertension and arteriosclerosis	Ventricular slowing and fibrillation
13. C. G.	♂	71	No	Hypertension and arteriosclerotic disease	Ventricular slowing and standstill; auricles continued for short time
14. M. L.	♀	27	Yes	Subacute bacterial endocarditis and patent ductus arteriosus	Ventricular slowing and standstill
15. I. F.	♂	52	Yes	Constrictive pericarditis, remote infarct	Ventricular slowing and standstill
16. M. T.	♀	49	No	Hypertensive cardiovascular disease, ? Dissecting aneurysm	Ventricular slowing and standstill
19. A. G.	♂	65	No	Gastrointestinal bleeding. Acute infarct	Sudden ventricular fibrillation
20. A. W.	♂	39	No	Arteriosclerotic heart disease and recent infarct	Ventricular slowing and standstill
21. A. S.	♂	73	No	Prostatism, anginal history, op. death	Sudden ventricular fibrillation
22. W. H.	♂	50	Yes	Hypertension, cardiovascular disease, recent and old infarcts	Sudden ventricular fibrillation
23. J. M.	♂	87	Yes	Aortic stenosis, Stokes-Adams Syndrome	Ventricular slowing and fibrillation

Summary: Sixteen cases, seven ventricular fibrillation

the eight patients with recent or old myocardial infarction, four died suddenly as a result of the abrupt onset of ventricular fibrillation, while the other four patients died suddenly with slowing and abrupt standstill. Fifteen of the sixteen patients with diseased hearts died rapidly. In only five of these was death directly due to the onset of ventricular fibrillation.

DISCUSSION OF THE LITERATURE, EXPERIMENTAL WORK, AND OUR CASES

Sudden Death.—We have reviewed the literature, which is summarized briefly in Table III. Including our cases, eighty cases of heart disease were noted while seventy-six patients died of other causes. Thirty-one of the heart cases and twenty-six of the other cases terminated in ventricular fibrillation. On careful study of the cases, we found only eight in which sudden death was directly due to the onset of ventricular fibrillation. An equal number of deaths were

TABLE III. PREVIOUS REPORTS OF THE TERMINAL ELECTROCARDIOGRAM

AUTHOR	YEAR	TOTAL CASES	HEART DISEASE	VENTRICULAR FIBRILLATION	OTHER DISEASES	VENTRICULAR FIBRILLATION
1 Robinson ³³	1912	7	0	0	7	1
2 Halsey ¹¹	1915	1	0	0	1	1
3 Dieuaide and Davidson ⁵	1921	2	2	0	0	0
4 Schellong ³⁴	1923	6	3	0	3	2
5 Willius ⁴³	1924	4	2	2	2	1
6 Kahn and Goldstein ²⁰	1924	7	4	0	3	2
7 Reid ³²	1924	1	1	1	0	0
8 Martini and Sckell ²⁵	1928	17	8	2	9	0
9 Turner ²⁸	1931	4	4	0	0	0
10 Hamilton and Robertson ¹²	1933	1	1	1	0	0
11 Meyer, P. ³⁰	1934	1	1	1	0	0
12 Calandre and Rodrigues ³	1934	1	1	1	0	0
13 Duvoir and Pollet ⁶	1934	2	0	0	2	1
14 Herles ¹⁶	1934	10	6	3	4	2
15 Laubrey and Degos ²³	1934	6	0	0	5	0
16 Buccianti ²	1934	*				
17 Jezer, et al. ¹⁹	1936	2	2	0	0	0
18 Vela ³⁹	1935	1	1	1	0	0
19 Misao, et al. ³¹	1937	(30)	?	(9)	?	—
20 Sigler, et al. ³⁵	1937	20	10	3	10	4
21 Hanson, et al. ¹⁴	1937	25	7	2	18	8
22 Grieco and Schwartz ¹⁰	1938	1	1	0	0	0
23 Smith ³⁶	1939	1	1	1	0	0
24 Levin ²⁴	1939	2	0	0	2	0
25 Goodrich and Needles ⁹	1940	2	2	1	0	0
26 Fritzche ⁸	1940	1	0	0	1	0
27 Thompson ³⁷	1941	1	1	1	0	0
28 Franke ⁷	1942	*				
29 Likoff, et al. ²⁵	1944	3	3	1	0	0
30 Krell ²²	1944	1	1	1	0	0
31 Marchand and Finch ²⁷	1944	2	0	0	2	0
32 Volini, et al. ⁴⁰	1945	2	2	2	0	0
33 Stroud and Feil	1947	23	16	7	7	4
Totals		187	80+	40	76	26

*Paper not available.

due to standstill of the heart. In all these cases, the history or necropsy findings showed coronary heart disease.

Harris^{15b} points out in his paper on acute experiments in dogs that occlusion of a coronary arterial branch for ten minutes will result in ventricular fibrillation in about 50 per cent of the cases, either initially or upon release of the occlusion. The cause of the ventricular fibrillation is due to rapid, repetitive ectopic systoles that shorten the period of refractoriness and/or slow conduction.^{15a} It must be remembered that two important differences exist between our series and that of Harris. First, he is dealing with animals in which the coronary arteries and myocardium are presumably healthy before the experiment, while our cases of heart disease are obviously abnormal. Second, in dogs the induction of ventricular fibrillation results in permanent fibrillation unless defibrillation is performed.⁴² In human subjects, ventricular fibrillation is not necessarily a permanent event, as there are a number of case reports in which spontaneous return to regular rhythm has been noted. In the literature we reviewed, although no recoveries occurred, a small number of the patients returned to orderly ventricular excitation after the burst of ventricular fibrillation.

Slow Death (Anoxic and Hemorrhagic Shock).—From our cases and those in the literature a fairly consistent pattern evolves. However, many exceptions prove the rule and no prediction can be made from the clinical findings in an individual case as to the terminal electrocardiographic patterns. The sequence of events is as follows: The initially rapid rate with sinus rhythm slows. Ectopic supraventricular beats may arise. There is prolongation of the auriculoventricular conduction time. Then excitation is initiated in the A-V node. Next, auricular activity ceases as the ventricular pacemaker develops. At this time, if many ectopic ventricular foci become active, ventricular flutter and fibrillation may ensue. Then, either the rate slows and the heart stops, or the rate increases and again a flutter-fibrillation may occur. In rare instances, auricular waves may be seen after all ventricular activity has ceased. The QRS widens and is reduced in amplitude. The T wave becomes larger and if inverted, becomes upright. Finally, the QRS and T merge into a monophasic, positive wave. The α wave of Shellong³⁴ can sometimes be seen between the QRS and T waves. It is usually upright. If auricular fibrillation was present previously, the rate slows and a regular nodal rhythm occurs. Auricular fibrillation rarely occurs. Dissociation of auricular and ventricular waves may occur. The most extreme example was cited by Fritzche⁸ in which three different ventricular waves occurred independently. Two of them probably represented "partial systole" in which a small, localized area of ventricular muscle beat independently of the main muscle mass. In summary, then, the course of events is sinus slowing, nodal rhythm, ectopic ventricular systoles, ventricular rhythm, slowing, and stoppage. Ventricular fibrillation occurs usually when there is ventricular tachycardia and ectopic ventricular beats or following a period of asystole.

Harris^{15b} has shown experimentally (in dogs) that the pattern we have described is seen in prolonged anoxemia or hemorrhage with the induction of shock. He has shown that sectioning of the vagus nerves will prevent the slow-

ing initially. He also showed that eventually the pattern will occur even with sectioning of the vagus nerves and suggests that it is then a local anoxic and metabolic reaction.

Therapeutically, in anoxic emergencies where the individual is otherwise in good condition generally, the vagal implication suggests that the use of atropine may prevent cardiac standstill.

SUMMARY

1. Twenty-three cases in which terminal electrocardiograms were observed have been reviewed in conjunction with a review of the literature and experimental work.

2. The electrocardiographic pattern of anoxic and/or hemorrhagic shock and the role played by the vagus nerves were described.

3. The terminal electrocardiogram showed ventricular complexes which were usually aberrant in form and slow in rate. Permanent standstill occurred without ventricular fibrillation in 50 per cent of the cases.

4. We have reported eight sudden deaths associated with coronary heart disease and found an equal number in the literature. Of the sixteen deaths, eight were due to a sudden burst of ventricular fibrillation and eight to sudden ventricular standstill.

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THE CHANGING INTENSITY OF THE FIRST SOUND IN AURICULAR FLUTTER, AN AID TO THE DIAGNOSIS BY AUSCULTATION

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THE bedside diagnosis of auricular flutter is generally regarded as being difficult or impossible to make with any degree of accuracy. In most instances, its recognition first becomes apparent after electrocardiographic study. There are, however, some findings which lead one to suspect its presence, and with increased experience, even definite diagnoses can be made.

When the heart rate is rapid and regular (130 to 170) and carotid sinus stimulation produces some temporary slowing followed by an irregular and "jerky" retreat to the former regular rate, auricular flutter is likely to be present (Fig. 1). If the heart rate is slow and regular and the possibility of auricular flutter is kept in mind, a brief exercise test may reveal the true nature of the abnormality. The rate may suddenly double (that is, change from 70 to exactly 140), or it may become rapid and irregular. In both instances, the increased rate is likely to return to the previous slow regular rhythm in a few minutes on resting (Fig. 2). The test can be employed if the heart rate is already irregular, as it may become more rapid and perfectly regular on exercise (Fig. 3), whereas auricular fibrillation, with which it can be confused, will retain its irregular rhythm (Fig. 4). The effect of a deep inspiration may also prove valuable. Occasionally, this not only produces a slowing but causes the rhythm to become more irregular than is ordinarily observed in other conditions.

A further point that may be helpful in diagnosis is the actual rate of the tachycardia. If the rate is 190 to 200 and perfectly regular, it is extremely unlikely that flutter is present. The auricular rate would of necessity be either 190 to 200 with a 1:1 rhythm or 380 to 400 with a 2:1 block. The former possibility can be fairly well ruled out because 1:1 flutter is extremely rare and the auricular rate of 190 is too slow (if untreated). The latter is very unlikely because the auricular rate in flutter rarely exceeds 360 (except with thyrotoxicosis and during fever).

The purpose of this paper is to report our observations on a new sign which is commonly present in auricular flutter, that is, a changing intensity of the first sound. This phenomenon is similar to that observed in other conditions, and

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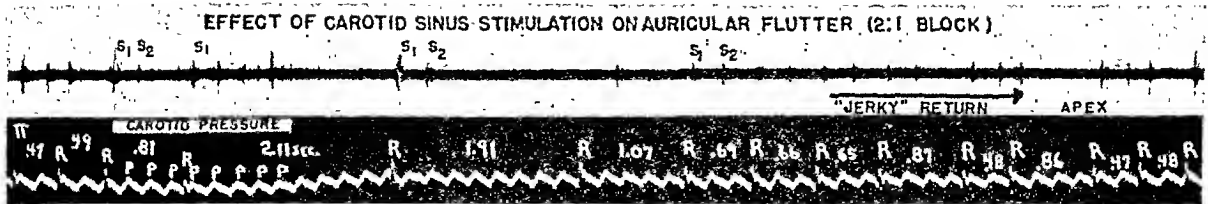


Fig. 1.—Carotid pressure produced prompt marked ventricular slowing, not affecting the flutter waves (*P*). Note "jerky" return to normal rhythm indicated by differences in R-R intervals. Patient was a 67-year-old man with paroxysmal auricular flutter.

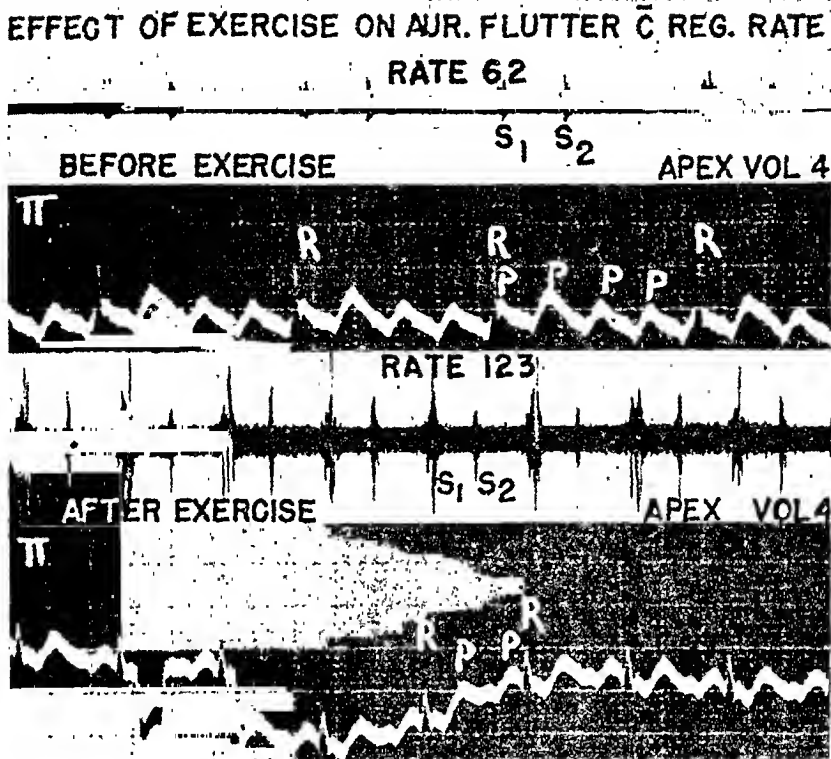


Fig. 2.—A 39-year-old man with paroxysmal auricular flutter. Note doubling of rate (62 to 123) after two minutes of exercise consisting of "hopping up and down." The mechanism changed from 4:1 block to 2:1 block.

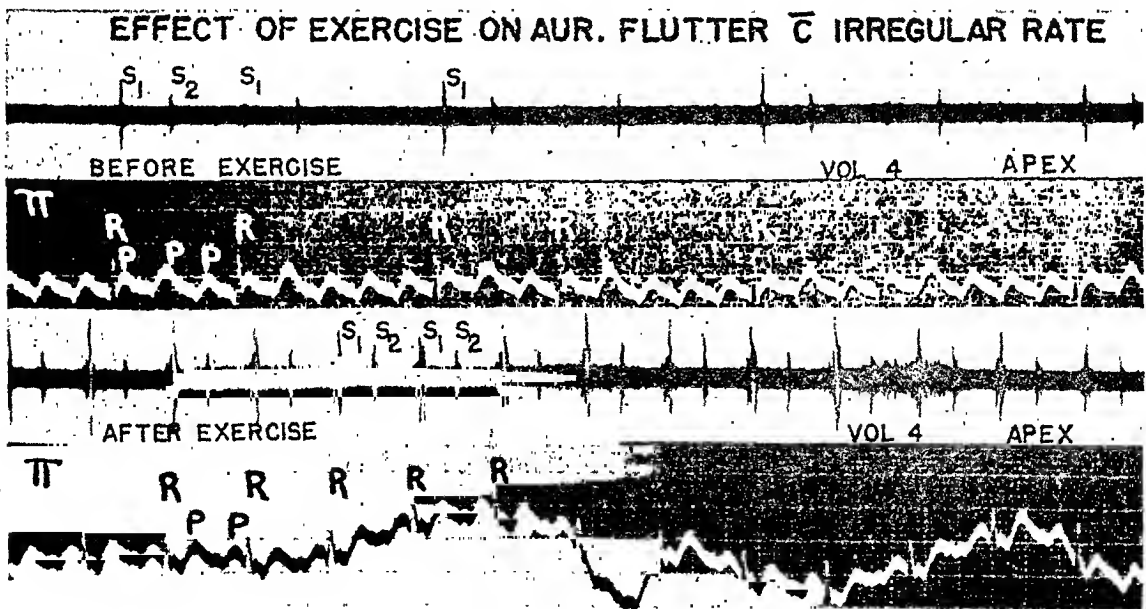


Fig. 3.—Note irregular rate (65) with flutter of varying block, 3:1, 5:1. Following exercise, the rate became regular (123) with a 2:1 block. A 39-year-old man with no organic heart disease.

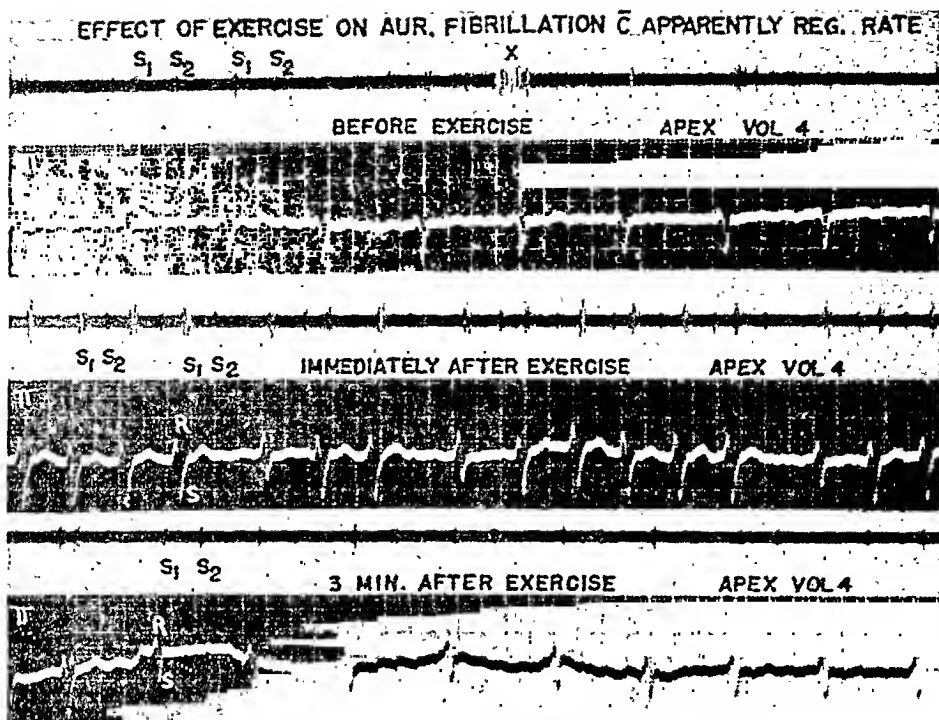


Fig. 4.—Upper tracing shows auricular fibrillation with only very slight irregularity. Heart sounds (S_1 , S_2) constant. Artefact (X) due to breathing. Exercise brought out irregularity (middle tracing). Three minutes later (lower tracing) heart had returned to original rhythm. This 59-year-old man had hypertensive heart disease with failure.

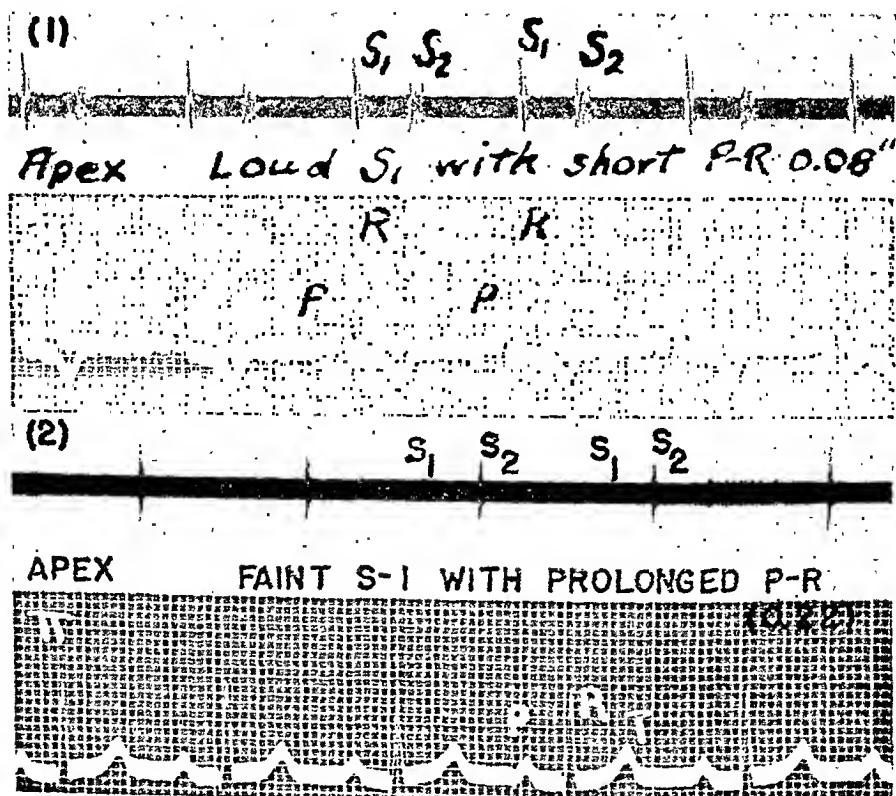


Fig. 5.—Upper tracing shows loud first sound (S_1) with short P-R interval (.08 second). Patient was a 24-year-old man with essential hypertension. Lower tracing shows almost inaudible first sound (S_1) with only slightly prolonged P-R (.22 second). Patient was a 24-year-old woman with Gaucher's disease.

the mechanism can probably best be appreciated by a brief review of the relationship of the P-R interval to the intensity of the first sound. Although this concept is not new,¹ it is apparently not generally known or has not been adequately stressed. When the P-R interval is prolonged, the first sound is usually diminished (Fig. 5). It is not necessary that the P-R be much prolonged, for even an interval of 0.21 second or 0.22 second will produce a faint first sound. This is a clinical means, and the only auscultatory finding that can lead to the suspicion of first degree heart block. Conversely, as one might suspect, when the P-R interval is short, the first sound is increased (Fig. 5).

The relationship of the P-R interval to the intensity of the first sound is well illustrated in Fig. 6. This patient with first degree heart block (P-R interval 0.28 second) had a faint first sound. Following intravenous injection of 1.0 mg. of atropine sulfate, the P-R interval was shortened to 0.18 second with a marked increase in intensity of the first sound, although the heart rate was unaltered. Complete heart block (Fig. 7) is another decisive illustration of this phenomenon, because in this condition the auricles and ventricles are beating independently with frequently changing P-R relationships. Again, it will be noted that when the P-R interval is short, the first sound is loud, whereas when it is lengthened, the first sound is diminished. When the P wave coincides exactly with the QRS complex, there may be no increase in the first sound. This changing intensity of the first sound in complete heart block, or the so-called "bruit de canon," is almost pathognomonic of this condition (an exception is shown in Fig. 9). This sign was first described by Strazhesko² in 1906, and later by Griffith³ in 1912. Additional light is shed on the problem by the observation that auricular fibrillation with a regular, idioventricular rhythm, such as occurs with overdosage of digitalis, shows a constant first sound (Fig. 7). This is in distinct contrast to the changing sounds in complete heart block at the same rate, and is added proof of the influence of auricular contraction on the intensity of the succeeding first sound. Another example is that of ventricular tachycardia. Here, also, the auricles and ventricles may be contracting independently. The changing intensity of the first sound in a tachycardia which does not respond to carotid sinus stimulation, especially if the rate is slightly irregular,⁴ leads one to make the correct diagnosis of ventricular tachycardia. In Fig. 8 the loud sounds are generally preceded by a short P-R interval, giving the complexes of the electrocardiogram coincident with the loud sound a configuration practically similar in each case. In fact, one can predict, without looking at the phonocardiogram, which complex will correspond to a loud first sound.

In this study we have noted that a changing intensity of the first sound is also common in auricular flutter. This observation was actually "stumbled upon" as a result of the examination of an 89-year-old man with carcinoma of the prostate. Auscultation of the heart revealed a slow, apparently regular rate of 42 per minute with a marked changing intensity of the first sound. Complete heart block was suspected, but carotid sinus stimulation produced an immediate and prompt slowing of the ventricular rate, which is unusual with complete block. The electrocardiogram revealed a regular 5:1 auricular flutter and the

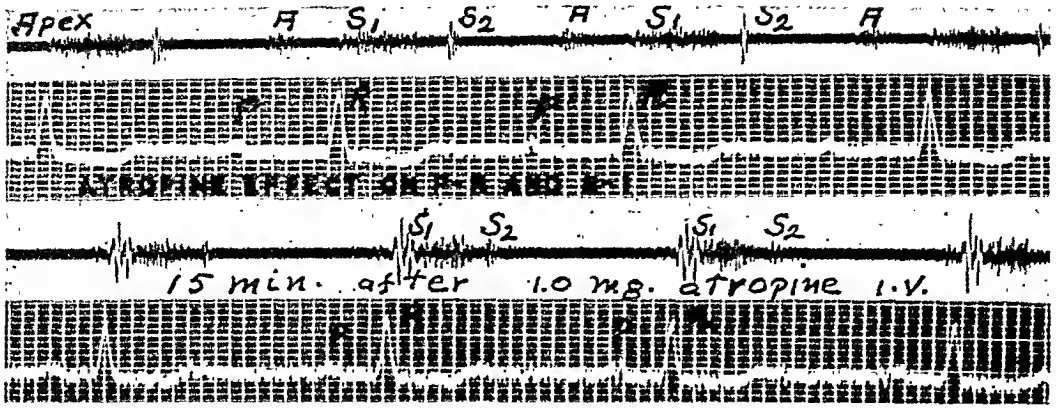


Fig. 6.—Upper tracing shows faint first sound (S₁) with long P-R interval (.28 second). Lower tracing shows loud first sound (S₁) fifteen minutes after 1 mg. atropine administered intravenously, when P-R interval was normal (.18 second). Auricular sounds (A) were detected in upper tracing.

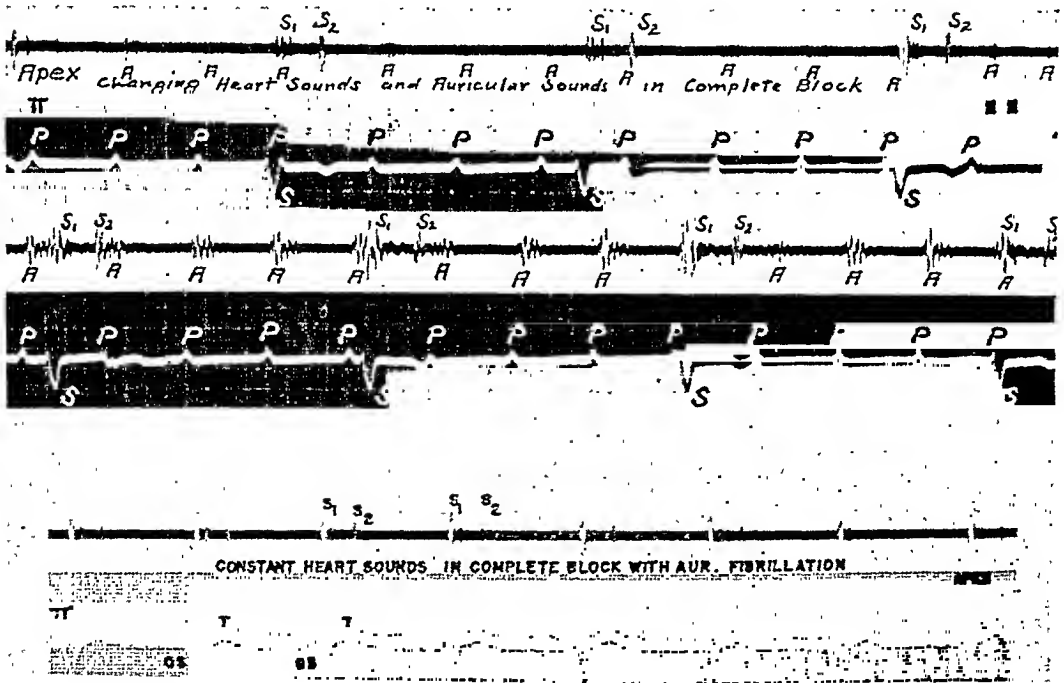


Fig. 7.—In upper tracing, note changing intensity of heart sounds, especially first sounds (S₁) in different cycles. Very loud are the sounds occurring with very short P-R intervals. When P and QRS occur simultaneously, first sound is not increased. Also note audible auricular sounds (A). Man, 75 years of age, had Adams-Stokes disease. In lower tracing, a case of complete block with auricular fibrillation shows no change in first sound. The auricles are not contracting and thus there is no P-R alteration.

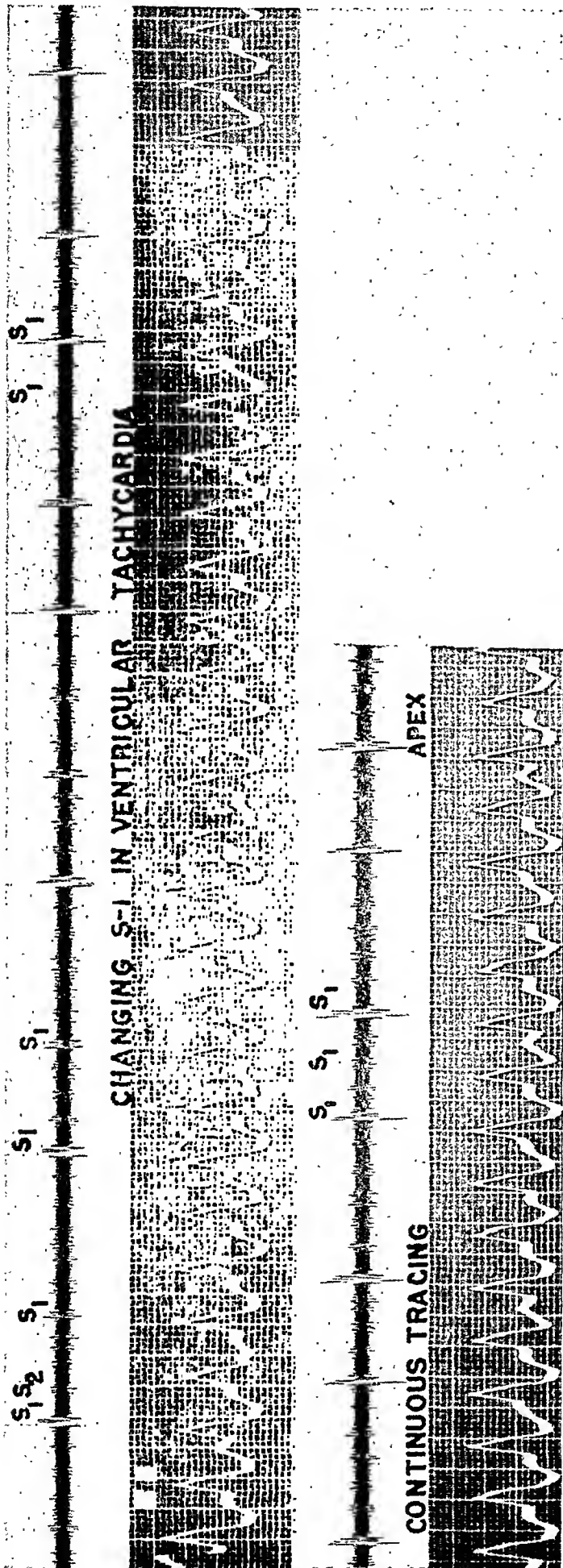


Fig. 8.—Note marked changing intensity of first sounds (S₁) with ventricular tachycardia. A changing P-R interval relationship is present. Each loud S₁ is generally preceded by ECG complexes almost identical in configuration. Patient was a 69-year-old man with Adams-Stokes disease.

phonocardiogram portrayed the changing intensity of the first sound noted clinically (Fig. 9). Careful measurement of the P-R intervals revealed that the ventricular response was not perfectly regular, but usually varied from 0.01 to 0.02 second in adjacent complexes. These minor differences, however, were sufficient to alter the over-all "P-R" relationship with the resultant change in the first sound. At other times, this patient was observed when his ventricular rate was noticeably irregular at the slow rate, and again, the first sound varied as before (Fig. 10).

In discussing the "P-R" relationship to the changing intensity of the first sound in auricular flutter, we purposely use quotation marks because of the obvious difficulty in deciding exactly where the "P" wave of auricular flutter begins. The differences of opinion as to whether the flutter wave begins with the upper peak, lowest point, or the "notch" on the down stroke has long been a controversial subject.^{5,6} This remains unsettled, but we feel that the "notch" actually represents the beginning. However, for convenience and ease of measurement, we have arbitrarily chosen as the beginning of "P" the lowest point of the wave preceding the QRS complex. The tip of the R wave has been designated "R." In this way we have attempted to correlate a changing "P-R" relationship to the changing intensity of the first sound in auricular flutter, similar in principle to that observed in complete heart block and ventricular tachycardia. Proof that such a relationship actually exists is shown in Figs. 9 and 10. When the "P-R" was in the range of 0.10 to 0.20 second, the first sound was loud, the loudest sound being at a "P-R" relationship of around 0.14 to 0.15 second. Above and below this range, the sounds were characteristically diminished. It is evident from the tracings that very slight changes in the P-R interval can cause marked differences in the intensity of the first sound. Using this or another arbitrary "P-R" measurement, similar results were noted in the other cases, although the "range" for loud first sounds varied with the individual case.

This first experience served as a stimulus to search for similar findings in other cases of auricular flutter. Since then, ten patients with auricular flutter have been studied. Although the phonocardiograph was used to obtain objective proof, in these cases simple auscultation with an ordinary stethoscope revealed the significant changes. The changing intensity of the first sound has been noted in all but two instances.* These two exceptions were not surprising, as it could be predicted that whenever the "P-R" interval remained constant the first sound would not change in intensity. Such events are known to occur when there is a pure and constant 2:1 or 4:1 A-V block in auricular flutter. This is well illustrated in Fig. 11. Examination of the phonocardiograms of flutter with constant sounds revealed that the "P-R" relationship also remained constant. Only when there was a difference in the ventricular response, even though slight, was there a change in the first sound (except for the minor changes produced by respiration).

*A third case (middle tracing of Fig. 11) showed constant sounds when in pure 4:1 block and changing sounds at other times (third strip in Fig. 13).

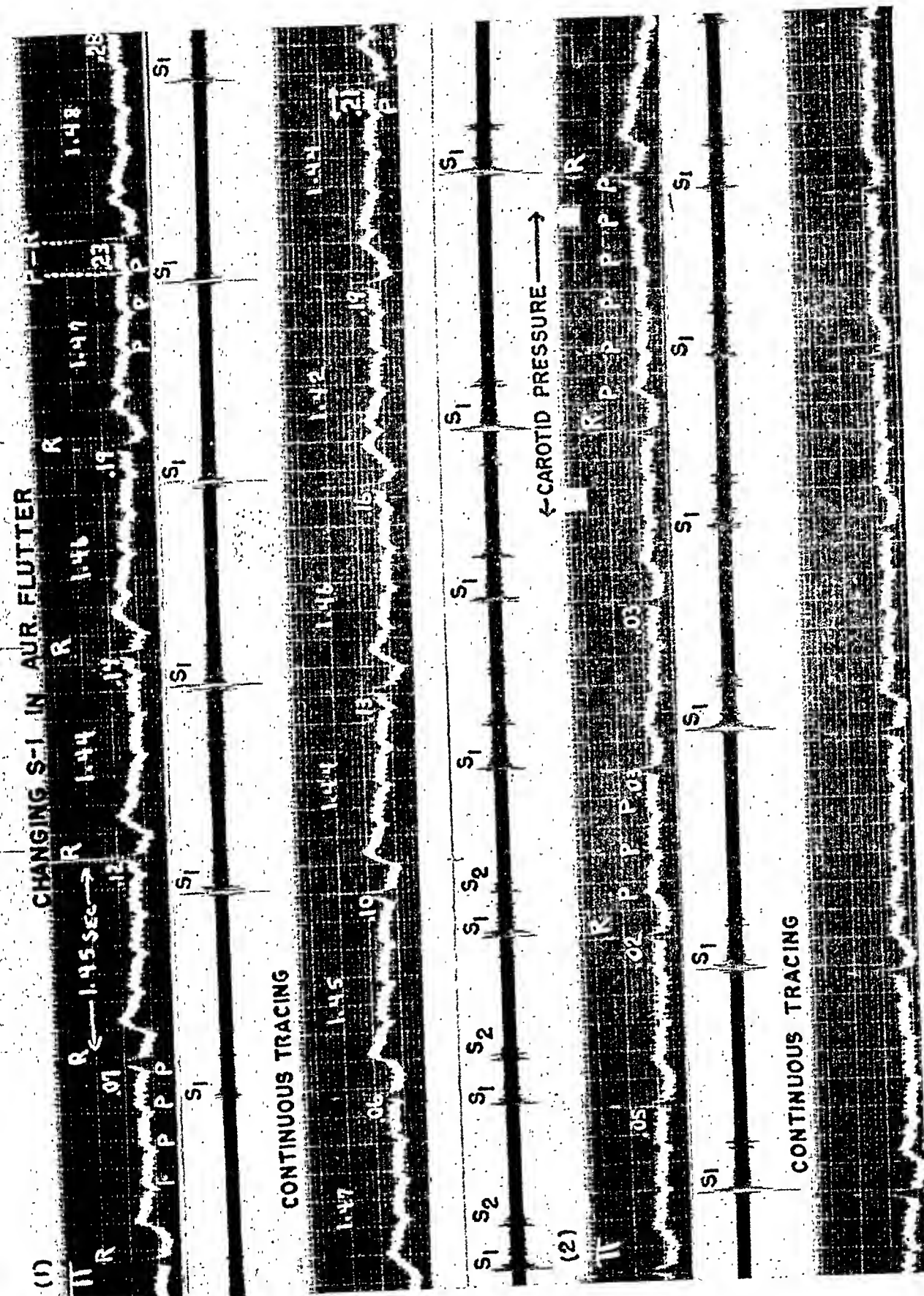


Fig. 9.—S₁ and S₂ are the first and second heart sounds. P, auricular flutter waves. R-R intervals and "P-R" intervals indicated in sounds. Note slight irregularity of ventricles and marked changing intensity of S₁. Loud first sounds generally occur in "P-R" range of .10 to .20 second. Lower two strips show ventricular slowing on carotid stimulation.

When there was a varying response in flutter such as 3:1, 2:1, and so forth, the first sound usually varied markedly, as would be expected. The loud sound, however, was not the result of a preceding longer diastole as is often noted in auricular fibrillation or following extrasystoles. The "P-R" relationship was

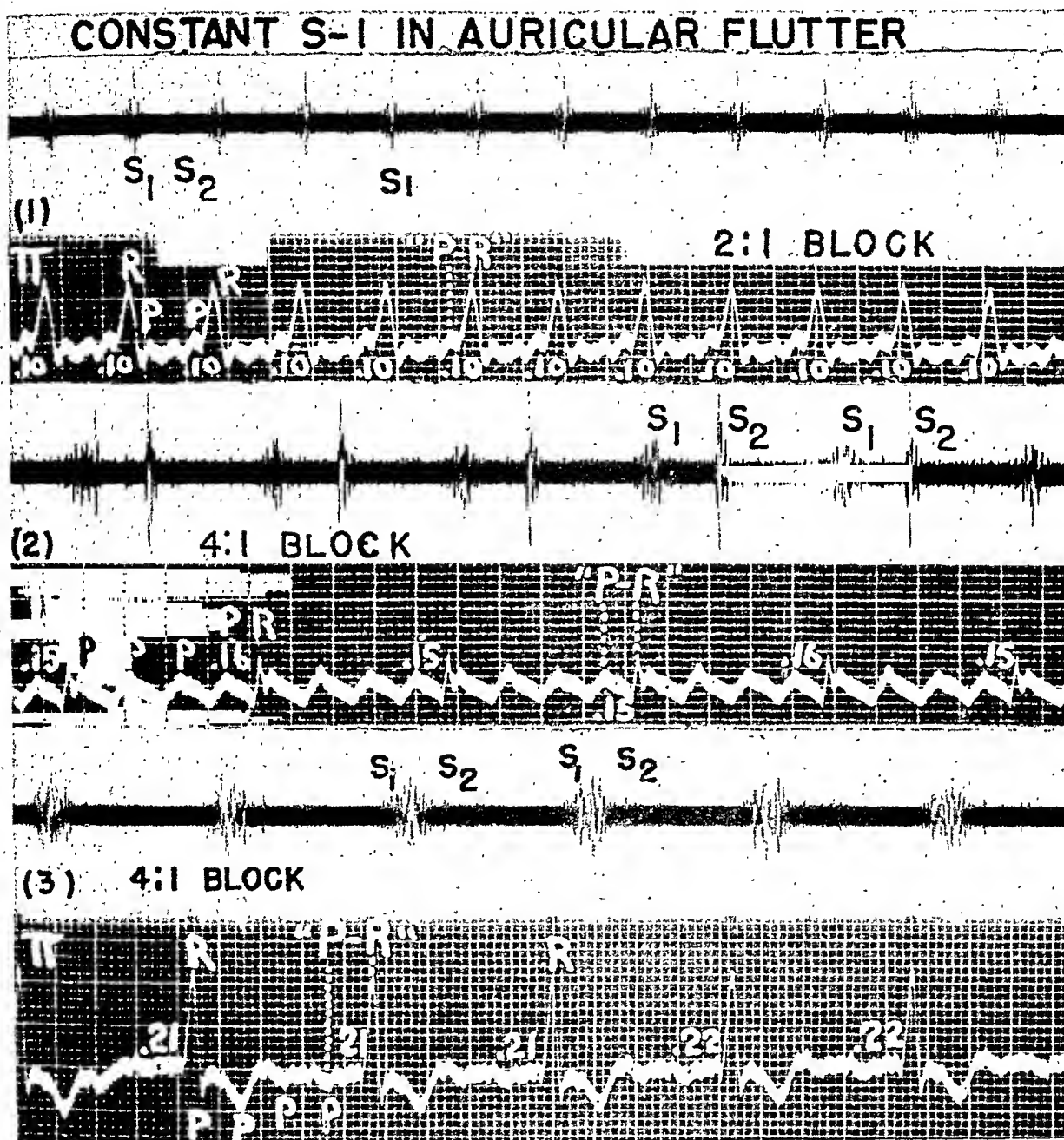


Fig. 11. — Three cases showing constant first sounds. The "P-R" interval in all cases remains practically constant. Note that P in the first and second case is arbitrarily measured from the peak of the flutter wave.

again the major factor as may be seen in Fig. 12. Here the loudest first sounds were those in a limited "P-R" range (in this case, about 0.19 to 0.24 second). When the first sounds did not fall in this "range" they were faint, even though the preceding diastole might have been prolonged.

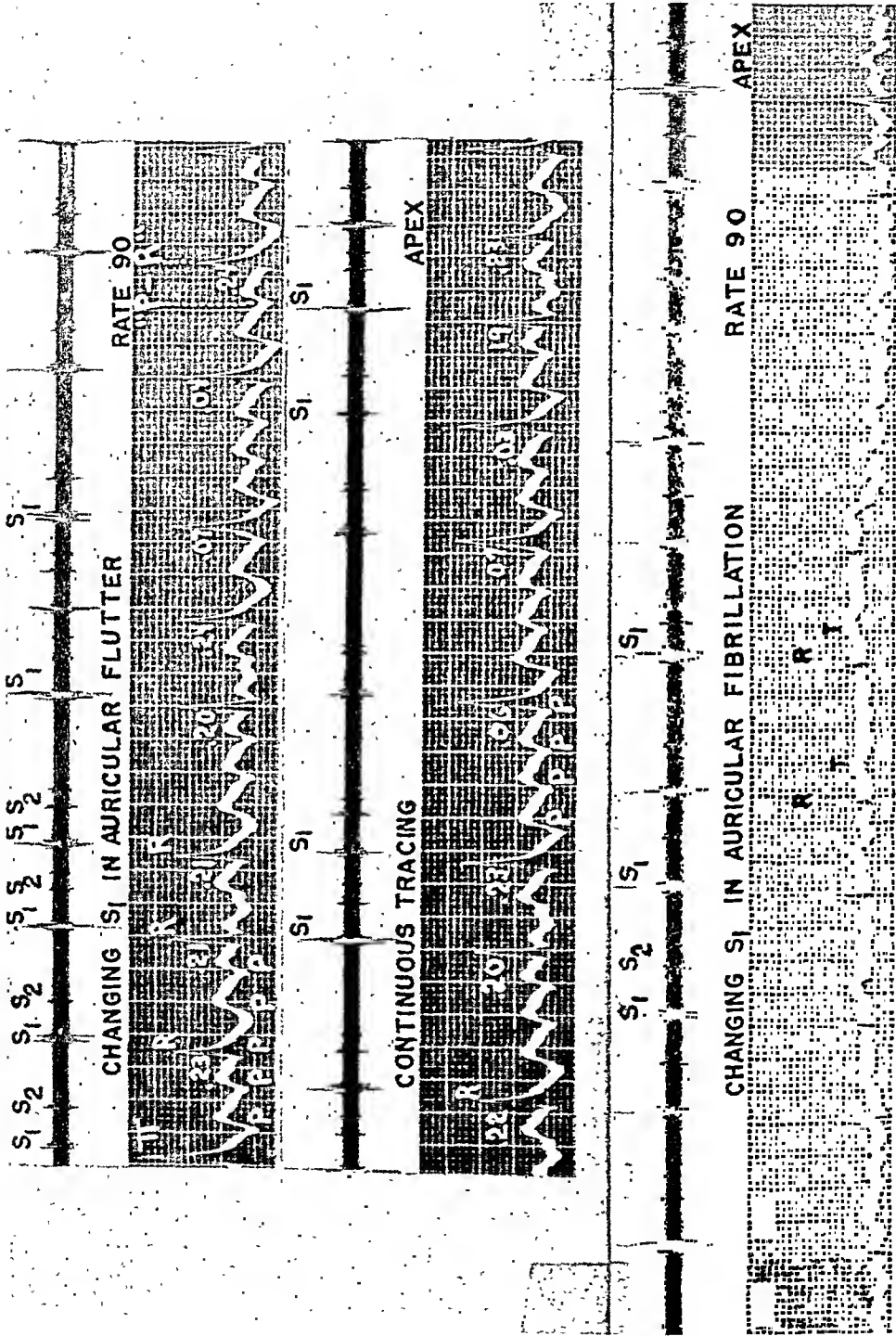


Fig. 12.—Note changing first sound (S₁) in upper tracing. Loud S₁ occurs in "P-R" range of .19 to .24 second with loudest at .20 second. Note faint S₁ with fourth and fifth complexes (second strip) which follow longer diastoles; seventh complex shows loud sound with short diastole. Lower tracing shows auricular fibrillation at same rate as above tracing with auricular flutter. The first sounds (S₁) are more constant with auricular fibrillation.

These observations help to explain the differences in the changes in intensity of heart sounds in auricular flutter and fibrillation. In the former, the auricles are actually contracting, whereas in the latter they are not. In fibrillation, therefore, the first sound should not vary in intensity as much from beat to beat, as the loudness of any heart sound would only depend on the length of the preceding pause and on the slight effect of respiration. In flutter there is the additional factor of auricular systole that has a much greater effect on the first sound. Fig. 12 shows a tracing of auricular flutter and one of fibrillation with the same ventricular rate. The changes in intensity of the first sound in the former are much greater than in the latter. Although it is realized that other factors may influence the intensity of the first sound, such as respiration, rate, length of diastole, and so forth, for reasons already pointed out, we do not feel, that they are of major importance in the changing first sound in auricular flutter. In fact, the respiratory effect was eliminated in the upper tracing of Fig. 12 as the phonocardiogram was taken while the breath was held in midexpiration. The same technique was employed in most of the other studies reported here. We believe, as has been emphasized by Dock,^{7,8} that the first heart sound is predominantly, if not entirely, valvular in origin, and is dependant to a great extent on the position of the A-V valves at the moment of ventricular systole. When the auricles contract just before the ventricles, the A-V valves are necessarily in a different position (deeper in the ventricles) than if they contract a longer time before the ventricles, when they may have already receded from their low position. It is logical to assume that the loudness of the sound will differ with changes in the position, which will be reflected in changes in the P-R interval.

In Fig. 13 are shown four cases of auricular flutter with changing intensity of the first sound. One might speculate that the first two cases resemble paroxysmal auricular tachycardia with block, but a study of other tracings, particularly during carotid sinus stimulation, made us regard them as instances of auricular flutter. Changing first sounds were noted in each of the four cases. Fig. 14 illustrates a case of 2:1 flutter with a changing first sound. Although the basic rhythm was 2:1 block, the ventricular response was not perfectly regular. Conduction to the ventricles from the perfectly regular auricles was not absolutely constant with each second cycle. The correct diagnosis of this case was made at the bedside on the basis of the auscultatory findings and the response to carotid sinus stimulation.

In addition, we have observed two cases of paroxysmal auricular tachycardia with block, apart from the two questionable cases illustrated in Fig. 13, which also showed changing first sound (Fig. 15). As in flutter, the "P-R" relationship was an apparent major factor. In fact, one would suspect that the findings in paroxysmal auricular tachycardia with block and auricular flutter would be alike in this respect, because of the underlying similarity of the two mechanisms.

In addition to the changing first sound, occasionally one may hear "extra" sounds during the cardiac cycle which correspond to auricular contractions.

CHANGING S-1 IN FOUR CASES OF AUR. FLUTTER

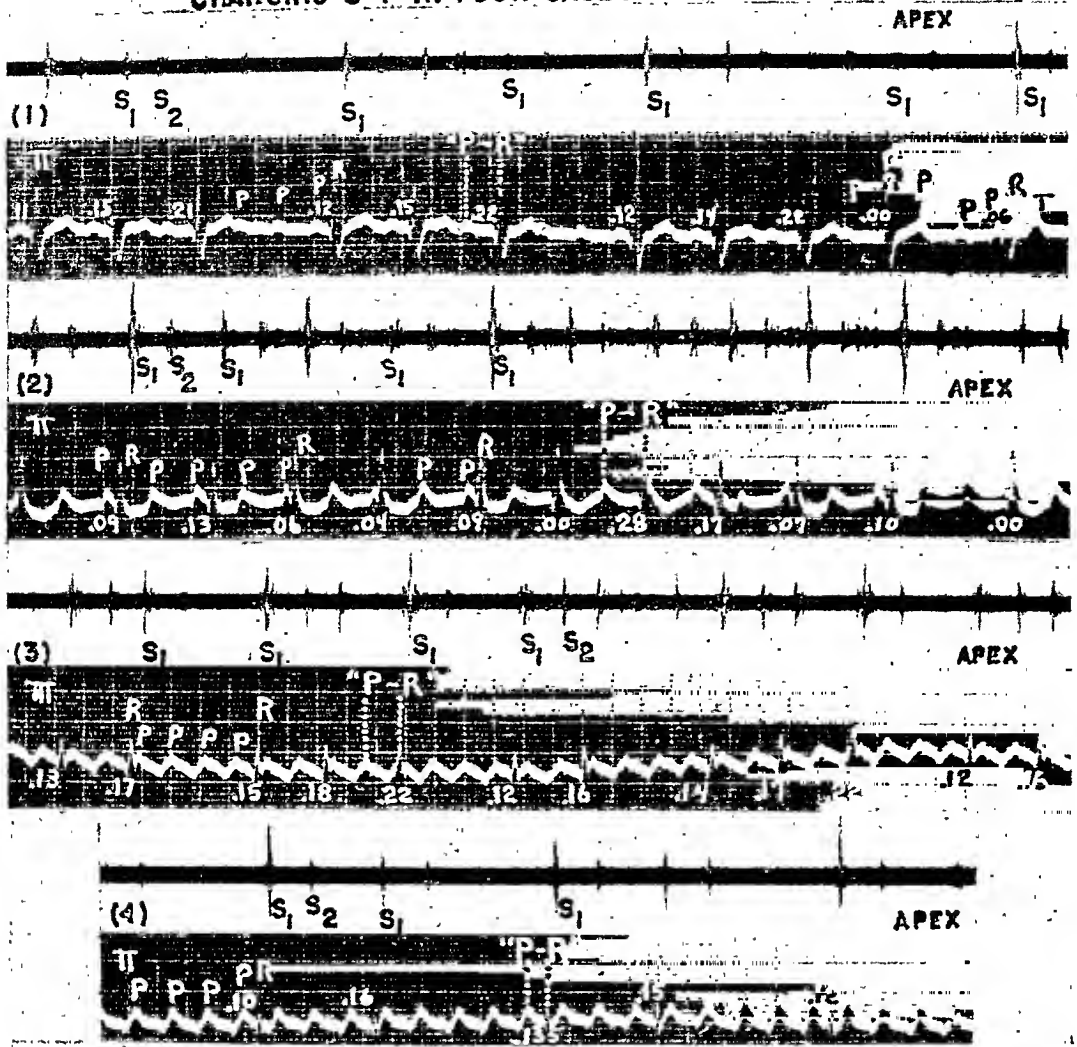


Fig. 13.— Four cases of auricular flutter showing changing first sounds (S_1). Note that the "P-R" interval in all cases is measured from the peak of the "P" wave. The loud first sounds occur in a "P-R" range of .06 to .12 second in the first case, .06 to .10 second in the second case, .22 second in the third case, and .10 to .13 second in the last case.

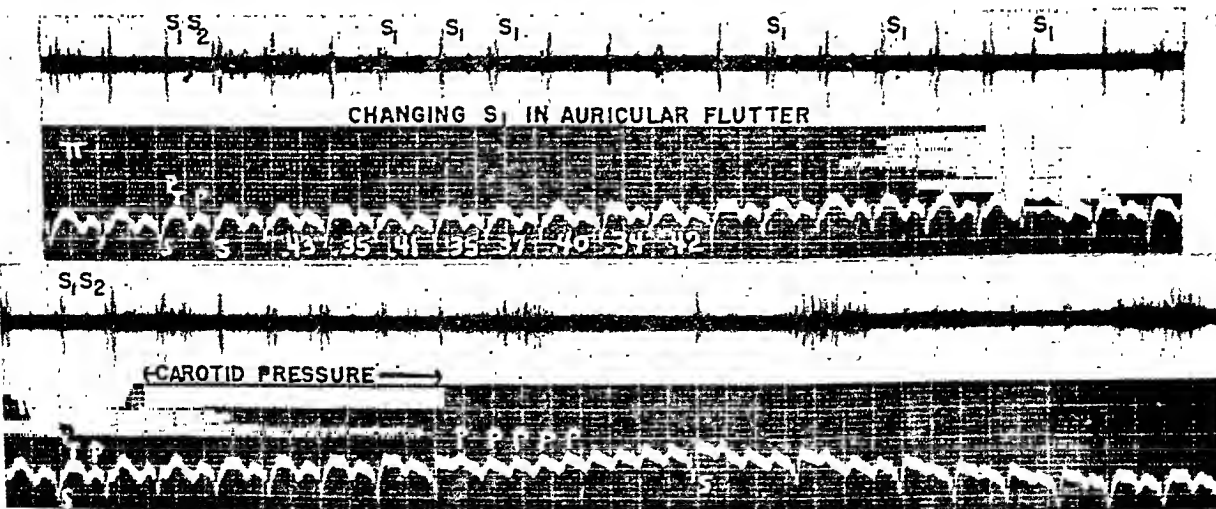


Fig. 14.— Man, 56 years of age, with 2:1 flutter following myocardial infarction. Changing intensity of first sound (S_1) noted clinically. The S-S intervals are not perfectly regular. Carotid pressure in lower tracing brings out the auricular waves (P).

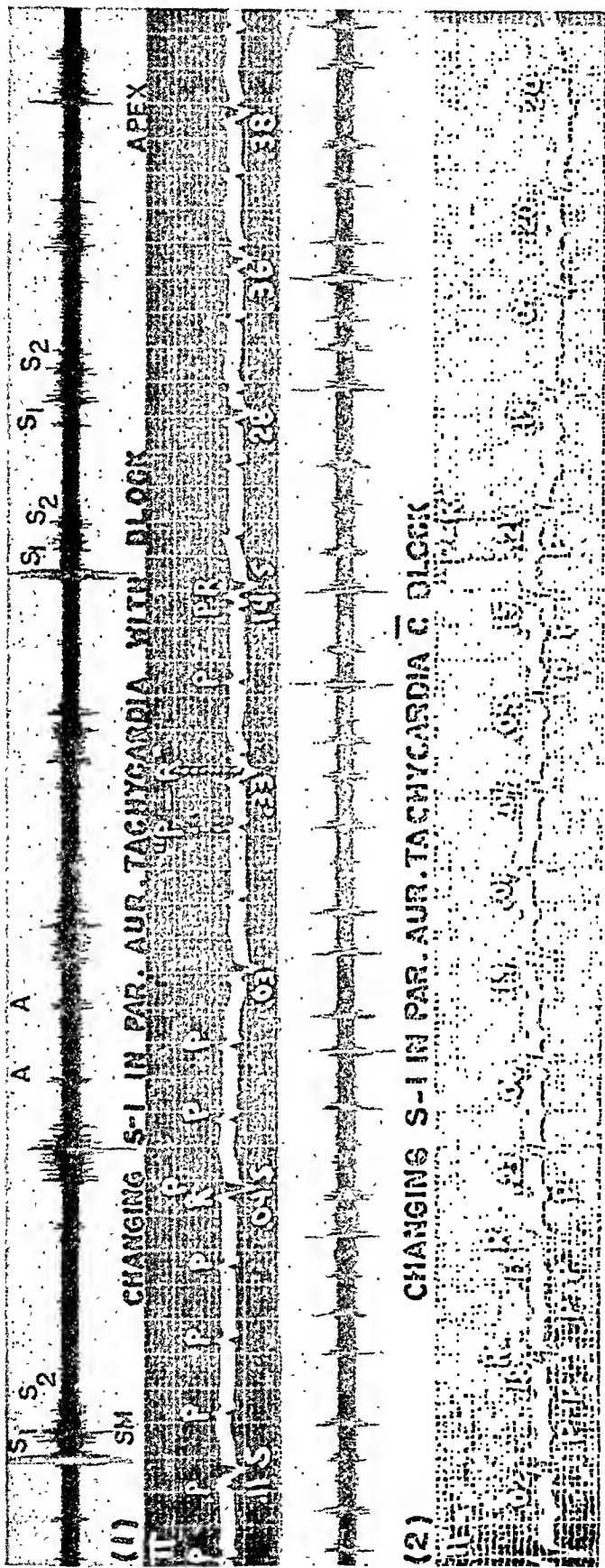


Fig. 15. —Two cases of paroxysmal auricular tachycardia with block. In upper tracing, note the marked change in intensity of the first sound, loud when the "P-R" range is 11 to 14 second. Auricular sounds (A) also noted. "P-R" interval in this case measured from peak of P to bottom of S. Lower tracing shows loudest first sound (S₁) when "P-R" is .06 to .09 second.

Such auricular sounds in flutter have been described and photographed by previous observers.^{9,10} The sounds may appear during systole (between the first and second normal sounds) or in different parts of diastole (Fig. 16). In one instance, the extra sounds were so prominent that they made some observers believe auricular fibrillation was present, though the true ventricular rate was rather slow and almost regular.

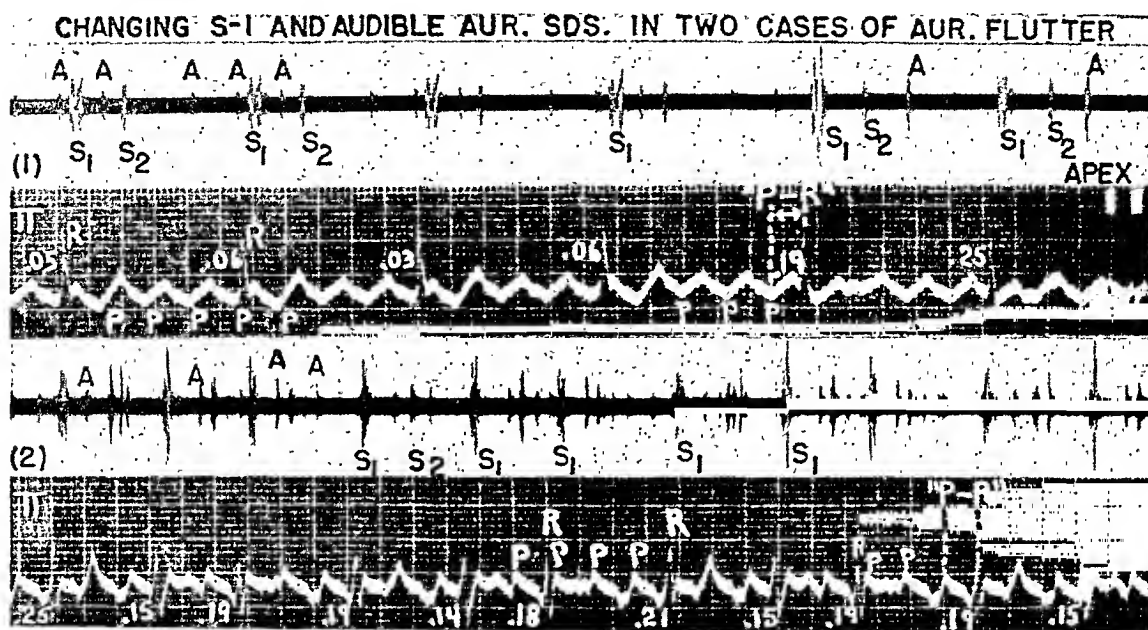


Fig. 16.—In upper tracing note almost regular rhythm with marked increase in intensity of the first sound (S₁) when "P-R" is .19 second. Audible auricular sounds (A) occur during systole (between S₁ and S₂) as well as during diastole (S₂—S₁). Note auricular sounds in last two complexes are louder than second sound (S₂). Woman, 32 years of age, with rheumatic heart disease. Lower tracing (Case 2): "P-R" range of .14 to .15 second results in loudest S₁. Audible auricular sounds also present in systole and diastole. Basic rhythm irregular. Man, 60 years of age, with rheumatic heart disease.

We believe that the auscultatory findings which have been discussed serve as an added aid to the bedside diagnosis of auricular flutter. They should prove valuable, especially when coupled with the other previously established methods of diagnosis. Although resort to the electrocardiograph may at times be indispensable in obtaining final proof, these simple signs may often enable the observer at least to suspect the presence of auricular flutter and at times to make a fairly definite clinical diagnosis.

SUMMARY

A new auscultatory sign has been observed in auricular flutter; changing intensity of the first heart sound. This phenomenon was present in eight cases where the ventricular response was irregular, although in some the degree of irregularity was very slight. In two instances where the rhythm was perfectly regular the first sound was essentially constant. It is thought that the changing intensity of the first sound is a result of a variation in the P-R interval similar

to the mechanism of the changing intensity of the first sound in complete A-V block and ventricular tachycardia.

These observations support the hypothesis that the first heart sound is mainly, if not entirely, valvular in origin and is dependent to a great extent on the position of the A-V valves at the moment of ventricular systole, a concept proposed by Dock.

Other factors, such as respiration and length of diastole, which may influence the intensity of the first sound, were found not to be responsible for the alterations observed in this study.

Two cases of paroxysmal auricular tachycardia with block were also observed which showed a changing intensity of the first sound, the mechanism being similar to that of flutter.

Other methods that aid in bedside diagnosis are the slowing effect following carotid sinus stimulation or deep breathing, particularly when there follows a jerky or irregular retreat to the original rate, the effect of exercise which may exactly double the heart rate or temporarily cause the irregular rhythm to become rapid and regular, and the detection of additional "auricular" sounds coming in different parts of diastole and even during systole.

These new auscultatory findings, coupled with other bedside methods of examination, have been very helpful in the clinical diagnosis of auricular flutter.

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OXYGENATION STUDIES IN CONGENITAL PULMONARY STENOSIS

AN APPLICATION OF RECORDING OXIMETRY IN THE EVALUATION OF CARDIORESPIRATORY FUNCTION

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RECENTLY the Blalock-Taussig operation¹⁻⁴ has been performed in fourteen cases of tetralogy of Fallot at this hospital. Physiologic studies of pulmonary oxygenation were made in ten of these patients by means of recording oximetry, of which two representative cases are presented. The studies were carried out preoperatively, during surgery, and postoperatively. The data obtained afford a convenient measure of cardiorespiratory function. Consequently, the method should be useful for assaying the benefit derived from the operation. In addition, the recorded changes in the arterial oxygen saturation during surgery offer a valuable adjunct to the surgeon and to the anesthetist.

METHODS

The Millikan-Smaller oximeter,^{5,6} together with suitable recording apparatus described by Hemingway,^{7,8} was used to obtain continuously the relative changes in the patient's arterial oxygen saturation. Arterial blood was drawn at appropriate intervals during the oximetry to obtain absolute blood oxygen values for calibration of the oximeter tracings. This precaution is advisable, particularly in cyanotic patients, because of the lesser accuracy of oximetry in the lower saturation ranges.⁵

In the preoperative studies, the effects on the arterial oxygen saturation were determined under the following conditions: (1) altering the tension of oxygen in the inspired air (using room air and 100 per cent oxygen), and (2) standardized exercise.

During surgery, the patient's oxygenation was recorded throughout the period of anesthesia.

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Postoperatively, a similar procedure was carried out as in the preoperative test. Exercise was extended to obtain a significant effect on the saturation. For twelve hours prior to the tests the patient was kept in bed to insure a basal state.

CASE REPORTS

CASE 1.—An 11-year-old white boy, D. A., was admitted to University Hospitals on Sept. 18, 1946, with a history of cyanosis that had been noticed since the age of 5 years. During the past six years, the child's physical endurance had progressively decreased, cyanosis had become severe, and digital clubbing had developed. Within the three-week period prior to admission, the patient had several episodes of syncope and orthopnea. At the time of admission, the patient was able to walk only fifty feet before he was forced to rest.

Physical examination revealed a poorly nourished, poorly developed boy with dyspnea at rest. A deep cyanosis was present in the nail beds and mucous membranes. The skin showed a dusky appearance with a prominent superficial venous pattern. There was suffusion of the conjunctivae. Marked clubbing was apparent in the fingers and toes. Examination of the chest revealed no enlargement of the heart as determined by percussion; the rate and rhythm of the heart were regular. The first heart sound was reduplicated and the second heart sound was pure. Along the left sternal border a soft blowing murmur was audible which was loudest in the second intercostal space. The blood pressure was 90/80 in each arm. There was no sign of cardiac decompensation.

Laboratory data showed a hemoglobin of 21.2 Gm., red blood cells of 8,700,000, and hematocrit of 80 millimeters. Arterial blood showed an oxygen content of 12.33 volumes per cent and an oxygen capacity of 30.82 volumes per cent (saturation, 40.9 per cent). The carbon dioxide capacity of venous blood was found to be 51 volumes per cent. Blood chlorides were 582 mg. per cent and blood urea nitrogen was 12 mg. per cent. Electrocardiography showed right axis deviation with spiked elevations of the P waves. By x-ray and fluoroscopy the cardiac index was found to be within normal limits. There was noted an absence of fullness of the pulmonary conus and the right ventricle appeared enlarged. The aortic arch was on the right side. The vascular markings in the lung fields appeared decreased. A diagnosis of tetralogy of Fallot was made, and on Sept. 20, 1946, the Blalock-Taussig operation was performed in which the left subclavian artery was anastomosed to the left pulmonary artery.

Oximetry Studies.—

Preoperative (Fig. 1,A): The basal blood oxygen saturation was 40.9 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 40.9 per cent to 45.0 per cent over a period of fifteen minutes. When the patient was exercised by walking, the saturation of blood oxygen decreased to 35 per cent within four minutes. At this time, because of the patient's distress, 100 per cent oxygen was administered, and seven minutes were required for the saturation to reach the previous basal level of 40 per cent.

Operative Record (Fig. 1,B): Following induction of anesthesia consisting of cyclopropane-oxygen, the patient's saturation was increased to a recorded value of 42 per cent. A slight decrease was noted in the saturation when the chest was opened. On several occasions, the percentage of oxygen in the anesthetic mixture had to be increased to prevent decreases in the saturation. When the left subclavian artery-left pulmonary artery anastomosis was completed and the clamps released, the saturation was only 42.6 per cent. Since a saturation increase of greater magnitude had been expected, the anastomosis was re-inspected. Following probing of the anastomosis there was a rise in the recorded saturation to 47 per cent.

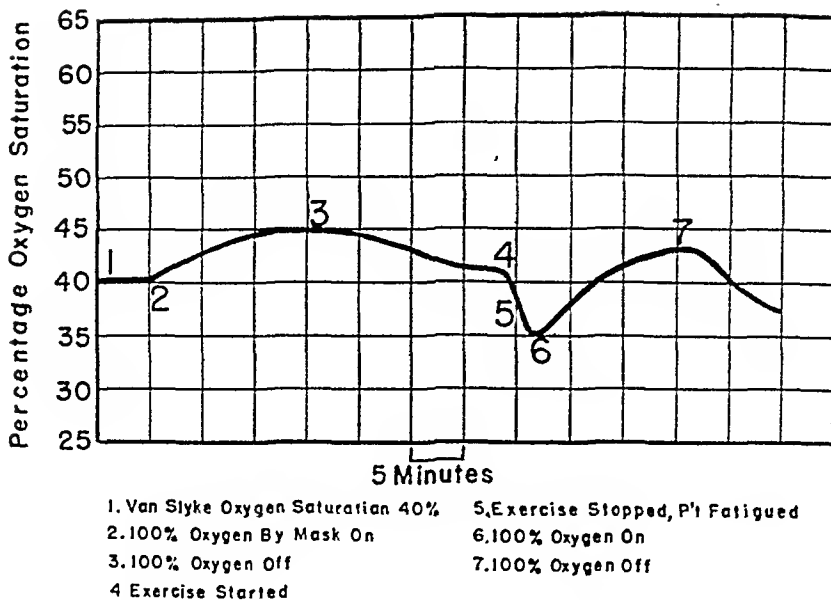


Fig. 1,A.—Case 1. Preoperative oximetry studies. See text for further description.

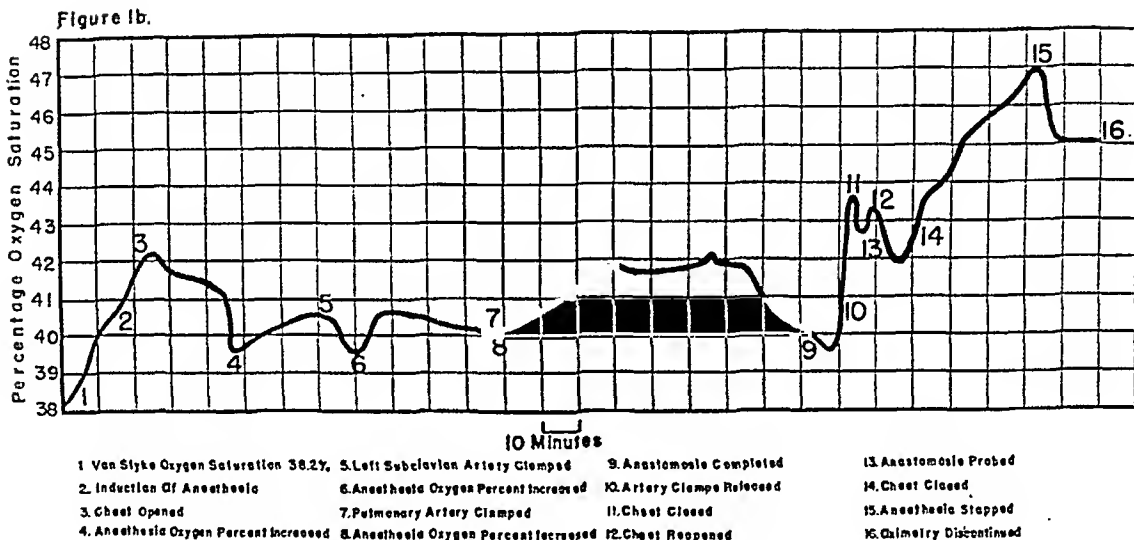


Fig. 1,B.—Case 1. Oximetry studies during operation.

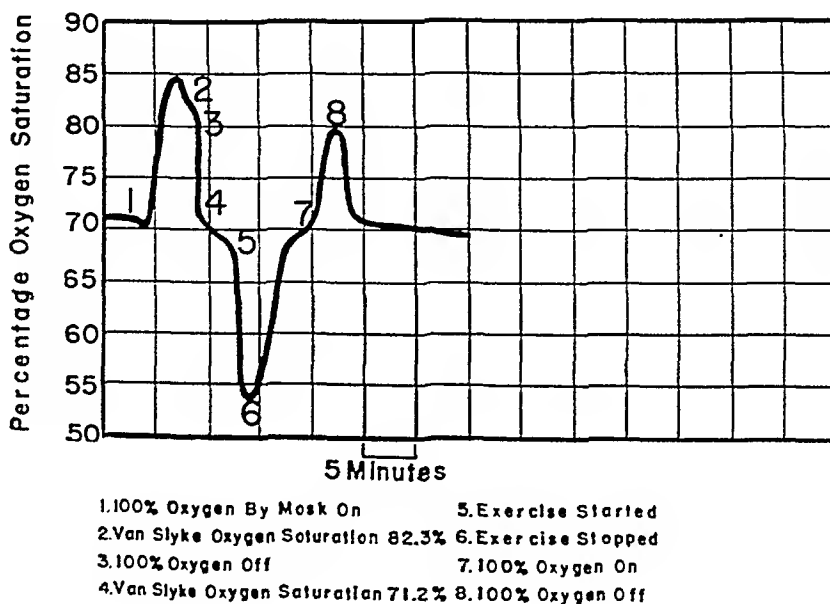


Fig. 1,C.—Case 1. Postoperative oximetry studies.

Postoperative (Fig. 1,C): This record was taken three months following operation. The basal blood oxygen saturation was 72 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 75 per cent to 85 per cent over a period of three minutes. When the patient was exercised as in the preoperative study, the saturation decreased to 53.5 per cent within two minutes. However, after five minutes of rest with the patient breathing air the saturation was restored to 70 per cent.

CASE 2.—A 5-year-old white girl, L. R., was admitted to University Hospitals on Sept. 30, 1946, with a history of cyanosis since birth. Since the age of 18 months, her condition had been diagnosed as congenital heart disease. She was able to take only a few steps before being forced to rest. There had been no episodes of unconsciousness.

Physical examination revealed the patient to be well developed and well nourished. The skin was plethoric and there was a deep cyanosis noted in the nail beds and mucous membranes. Moderate digital clubbing was present. Chest examination showed no cardiac enlargement to percussion; heart sounds were well heard, and no irregularities of cardiac rate or rhythm were found. Along the left sternal border a harsh systolic murmur and thrill were apparent with greatest intensity in the third intercostal space. Blood pressure was 104/84 in each arm.

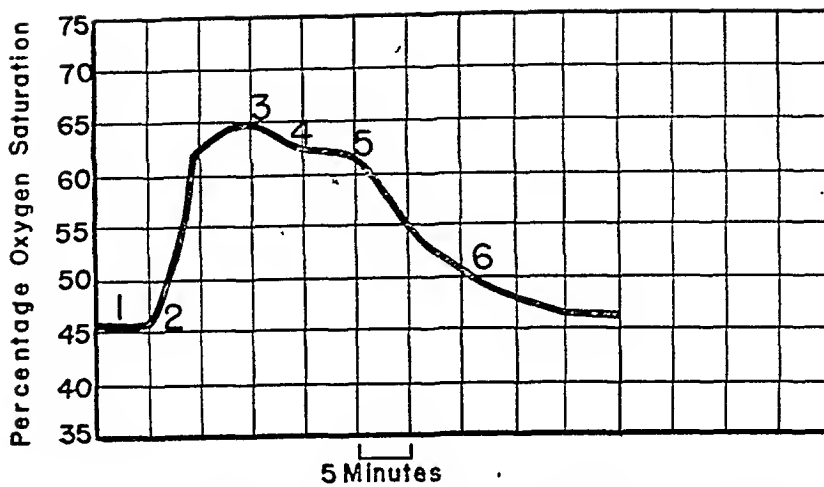
Laboratory data revealed a hemoglobin of 26.5 Gm., red blood cells of 9,840,000, and hematocrit of 82 millimeters. Arterial blood showed an oxygen content of 15.4 volumes per cent and an oxygen capacity of 35.49 volumes per cent (saturation, 43.5 per cent). Electrocardiography showed right axis deviation and spiked elevations of the P waves. By x-ray and fluoroscopy the cardiac index was found to be within normal limits. A concavity was noted along the left cardiac border, and there was right ventricular hypertrophy. The aortic arch and descending aorta were on the right side. A diagnosis of tetralogy of Fallot was made, and a Blalock-Taussig operation was performed on Oct. 3, 1946, at which time the innominate artery was anastomosed to the left pulmonary artery.

Oximetry Studies.—

Preoperative (Fig. 2,A): The basal blood oxygen saturation was 45.9 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 45.9 per cent to 65.0 per cent over a period of ten minutes. Exercise test was unsatisfactory because the patient was in severe distress upon slight exertion. When 100 per cent oxygen was withdrawn and the patient allowed to breathe room air, twenty minutes were required for the saturation to decrease to the previous basal value of 45 per cent.

Operative Record (Fig. 2,B): Following induction of cyclopropane-oxygen anesthesia, the saturation reached a recorded value of 67 per cent and remained above 60 per cent until the pulmonary artery was clamped. At this juncture the recorded saturation decreased to 55 per cent. Following completion of the innominate artery-left pulmonary artery anastomosis, removal of the clamps was followed by an increase in the recorded saturation to 71 per cent. At this time the patient developed peripheral vascular collapse suddenly, and the saturation decrease accompanying this shock was rapidly reversed by the administration of the intravenous plasma and 100 per cent oxygen.

Postoperative (Fig. 2,C): This record was taken five months following operation. The basal blood oxygen saturation was 78 per cent. Saturation response to the administration of 100 per cent oxygen showed an increase from 78 per cent to 88 per cent over a period of two and one-half minutes. When the pa-



1. Van Slyke Oxygen Saturation 45.5% 4. Van Slyke Oxygen Saturation 62.8%
 2. 100% Oxygen By Mask On 5. 100% Oxygen Off
 3. Started Crying 6. Stopped Crying

Fig. 2,A.—Case 2. Preoperative oximetry studies. See text for further description.

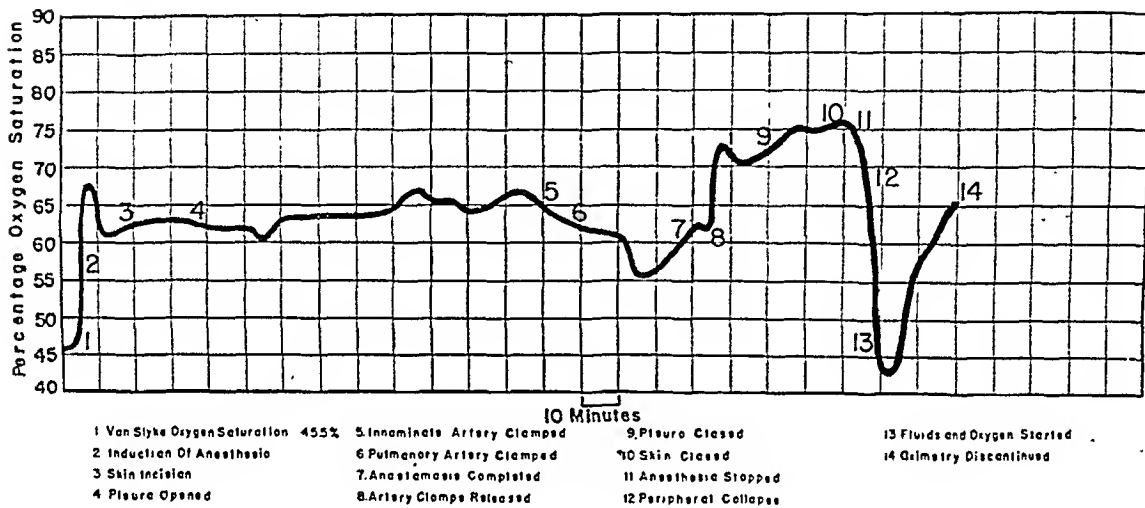


Fig. 2,B.—Case 2. Oximetry studies during operation.

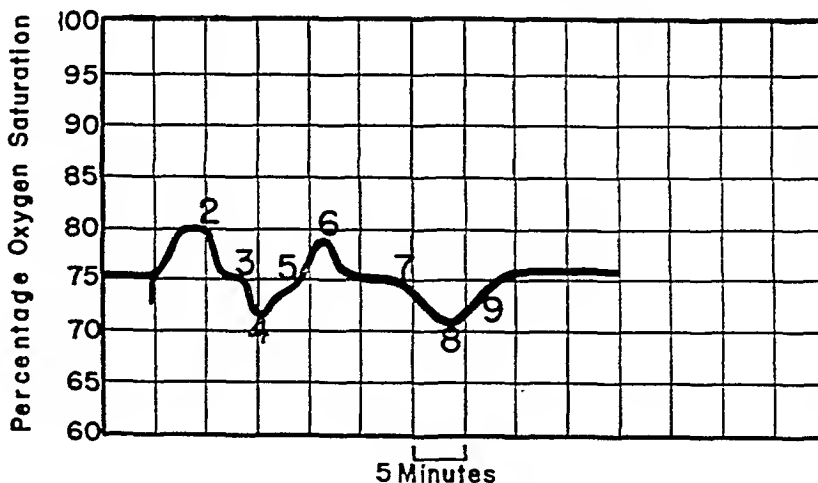


Fig. 2,C.—Case 2. Postoperative oximetry studies.

tient was exercised by walking, there was a decrease in the recorded saturation to 73 per cent within two minutes, and three minutes were required for the saturation to return to 78 per cent with the patient breathing room air.

DISCUSSION

The recording oximeter is a valuable instrument for studying oxygen saturation changes under various circumstances in patients with cyanotic congenital heart disease. To obtain the descriptive curves of the saturation responses by chemical analysis of arterial blood samples would be difficult, if not impossible, because of the many arterial punctures required. Because the physiologic adjustment postoperatively depends primarily upon the efficiency of the heart and lungs in supplying oxygen to the tissues, oximetry is an excellent method for obtaining this information directly. The complexity of vascular mixing in the cardiovascular system of these patients necessitates indirect measurement of cardiac output and total pulmonary flow postoperatively. Although oximetry does not provide these data quantitatively, the saturation responses furnish a valid measure of the success of the shunt operation.

It is believed that a very significant determination for evaluation of the operative success is the saturation time. This term refers to the time required to reach maximal arterial oxygen saturation when a subject is breathing 100 per cent oxygen. Recently, Fowler and Comroe¹⁰ have utilized oximetry to determine this interval in normal subjects. Their results indicate saturation time within three minutes. It is, of course, well known that a normal individual can fully saturate his arterial blood when breathing pure oxygen, while the average saturation is 97 per cent in the normal atmosphere. Preoperatively, in the cases studied in this series, the saturation time was prolonged three to four times over the normal, ranging from ten to fifteen minutes. Postoperatively, all patients were found to have saturation times within the normal range. More recently it has been possible to study three of Dr. Alfred Blalock's patients, who were six months, one year, and two years postoperative, respectively. All three reached maximal saturation within three minutes when breathing 100 per cent oxygen. It is significant, however, that the exercise tolerance postoperatively (in terms of the range of the saturation response) continues to indicate a limitation in the cardiorespiratory reserve function. This is not surprising when one remembers that the proportion of shunted blood increases appreciably with exercise. The last two mentioned patients, nevertheless, showed a maximal decrease in saturation of only five per cent with extended exercise.

The explanation of the increased saturation time preoperatively in these cases, as well as the return to normal postoperatively, is not clear at the present time. The remarkably great increment in peripheral oxygen saturation, which usually occurs in patients with tetralogy of Fallot while breathing 100 per cent oxygen, is equally difficult to explain.

One factor which has to be considered is an increased pulmonary capillary barrier. It is difficult to state whether or not a gradient between the alveolar oxygen tension and the oxygen tension in the pulmonary vein exists. However,

blood obtained from the pulmonary vein by catheterization in several cases of tetralogy of Fallot has shown an oxygen saturation of from 95 to 97 per cent. Therefore, this aspect is felt to be of no great importance in the present consideration.

Another important factor to be considered is the mixing of venous blood and fully saturated pulmonary venous blood in the right ventricle and aorta. If one assumes that the arteriovenous difference remains essentially constant, the arterial oxygen content could rise slowly, as a result of a gradual increase to a maximal level of the oxygen content of the mixed venous blood. To correlate this suggested hypothesis with the facts obtained by the oximeter, it will be necessary to obtain more simultaneous data.

The normal saturation time postoperatively must be related to the increased "effective pulmonary blood flow," which has been demonstrated by Bing, Vandam, and Gray.¹⁶

It is worthy of note that the two patients presented in detail responded differently to 100 per cent oxygen. Preoperatively, Patient 1 showed a rise of only 5 per cent in oxygen saturation, while Patient 2 rose 20 per cent. Postoperatively, Patient 1 rose 15 per cent, while Patient 2 rose only 10 per cent. However, both demonstrated the same changes in saturation time (which became normal after surgery) while being prolonged preoperatively. Oximeter studies on a greater number of patients will perhaps clarify this discrepancy or variability in range of maximal saturation attained when 100 per cent oxygen is administered.

CONCLUSIONS

The studies on arterial oxygen saturation reported at this time show two important facts. First, the rise in arterial oxygen saturation upon the establishment of the systemic-pulmonary arterial shunt was practically immediate; and second, the saturation time upon administration of 100 per cent oxygen was greatly shortened following surgery. The first observation indicated that the shunt had a direct primary beneficial effect on arterial oxygen saturation. The second would seem to show that the net effect of the operation was to increase the fraction of the total cardiac output supplying the pulmonary vascular bed. The implication from these observations is that the shunt resulted in a substantial improvement in the functional capacity of aeration of blood.

SUMMARY

1. The recording oximeter has been used to measure changes in arterial oxygen saturation in ten cases of tetralogy of Fallot. Detailed studies of two cases are presented.
2. The observations have shown immediate increase in arterial oxygen saturation and decrease in the saturation time after establishment of a systemic-pulmonary arterial shunt.
3. The significance of alterations in the saturation time has been discussed and a possible explanation presented.

4. The recording oximeter provides instantaneous information concerning arterial oxygen saturation during the course of surgical procedures involving the great vessels, and can provide the surgeon and anesthetist with valuable guides as to the condition of the patient during anesthesia.

We are indebted to Dr. M. B. Visscher, Dr. Allan Hemingway, and Dr. Irvine McQuarrie for their helpful advice and cooperation.

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WOLFF-PARKINSON-WHITE SYNDROME WITH MYOCARDIAL INFARCTION: AN EXPERIMENTAL STUDY

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THE Wolff-Parkinson-White syndrome, which shows an electrocardiographic pattern consisting of a short P-R interval associated with a wide QRS complex and abnormal T waves, has been recognized commonly in the past few years, and many case reports have appeared in the literature. More recently there have been several reports of the Wolff-Parkinson-White syndrome associated with myocardial infarction,¹⁻³ which is the subject of this paper.

METHODS

The experimental work was performed on cats according to a procedure previously outlined.^{4,5} In brief, this consists of picking up the auricular excitation wave by electrodes placed directly upon the right auricle in the open chest of a cat, amplifying these impulses, and passing them into a time-delay circuit. The output of the time-delay circuit is then used to stimulate the ventricles. In this manner an electrical short circuit between the auricle and ventricle is established by which any desired degree of premature stimulation of one ventricle can be accomplished; in other words, ventricular fusion beats are produced.

The term ventricular fusion is used to indicate excitation of the ventricles by two or more stimuli originating in different parts of the heart at approximately the same time and each causing contraction in a limited area of cardiac muscle. In the present work part of the ventricles are stimulated by the normal conduction system and part by the extra stimulus introduced prior to the time the ventricle is stimulated in the normal manner. The degree of fusion is thus a function of the prematurity of the artificial stimulation. If the artificial stimulus falls too early, all the ventricular muscle will be stimulated from this source alone, and the resultant beat will be a simple premature ventricular contraction. With proper timing of the premature artificial stimulus any desired degree of fusion may be obtained. In the present work fusion was studied before and after ligation of a coronary artery.

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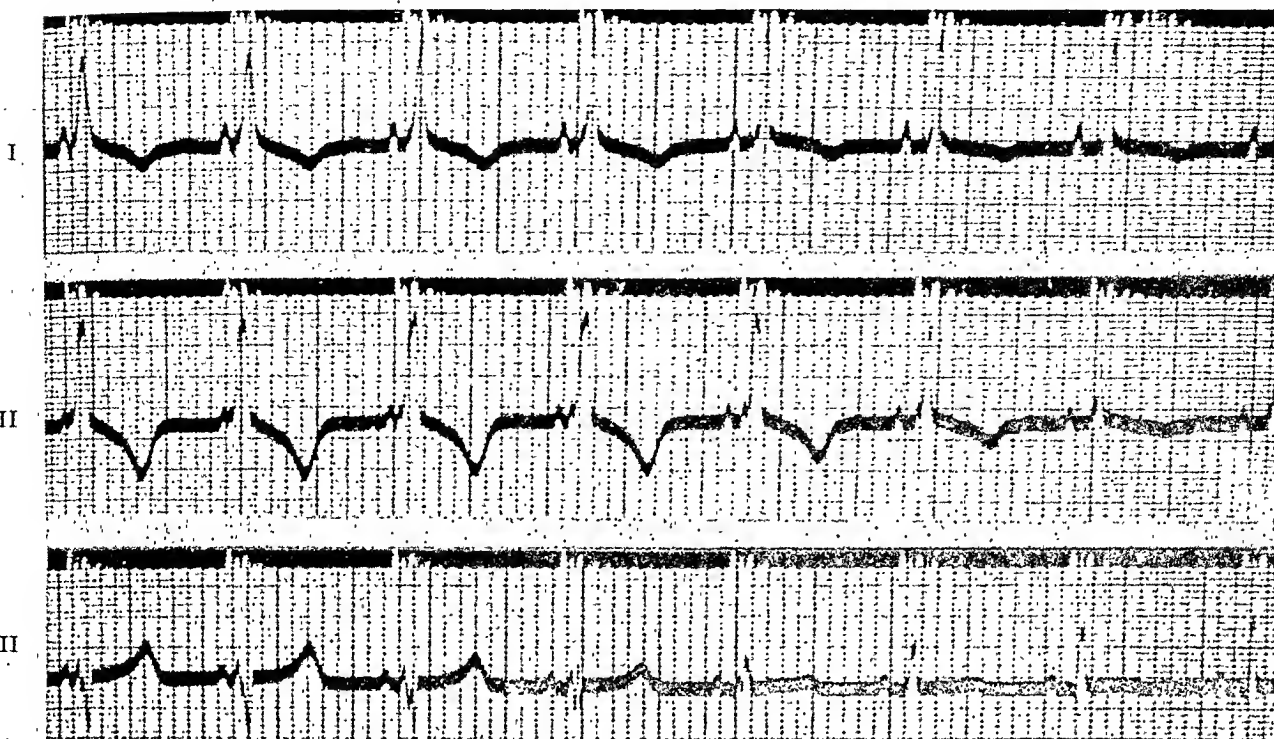


Fig. 1.—Cat No. 5. Fusion produced by variable pre-excitation of the right ventricle in the undamaged cat heart. On the right side are normal beats, while those on the left are premature ventricular contractions. Varying fusion is produced by gradually changing the amount of delay of the circuit stimulating the right ventricle. From the left to right there is a gradual increase in the P-R interval, a gradual narrowing of the QRS complex, and a gradual change in the magnitude of the QRS complex and the T waves, which is the result of ventricular fusion.

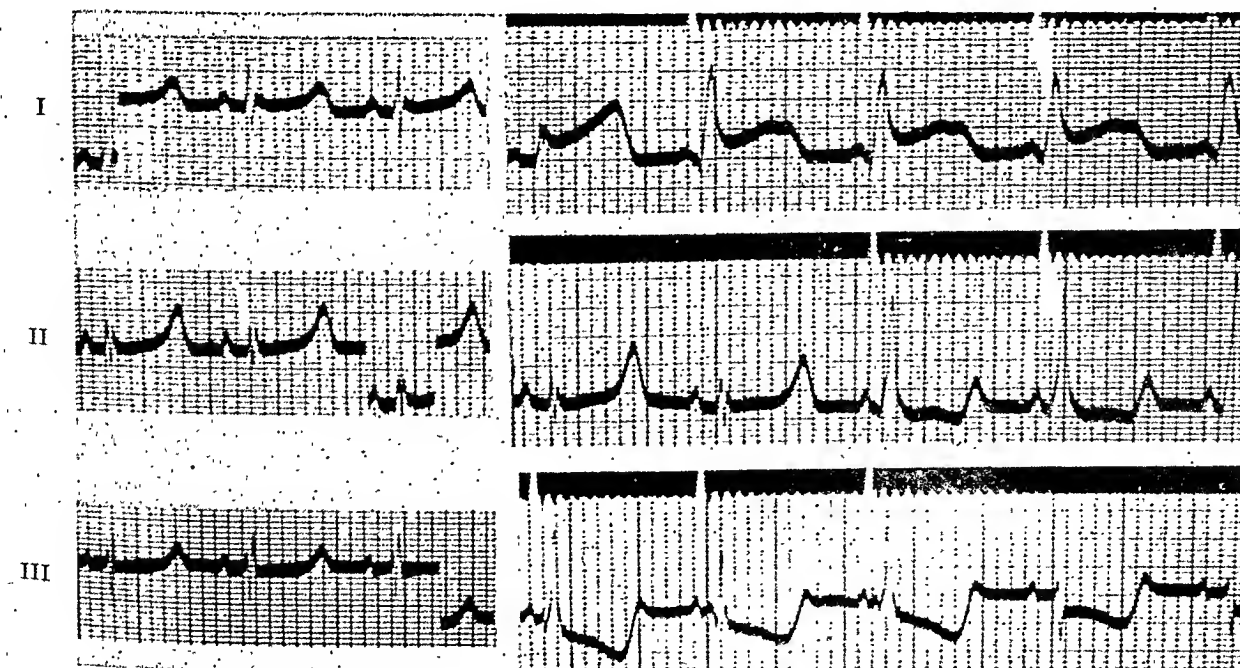


Fig. 2.—Cat No. 2. On the left are seen the standard leads before ligation of the anterior descending coronary artery in a cat. On the right side are the same leads after ligation. The break in the black line at the top of each tracing indicates the time of excitation of the right ventricle. Normal beats are present in each lead (Complex 1 in Lead I, Complexes 1 and 2 in Lead II, and Complex 4 in Lead III).

EXPERIMENTAL RESULTS

Fig. 1 shows fusion beats produced by variable pre-excitation of the right ventricle in the undamaged cat heart. With variation in the P-R interval, changes in the duration and character of the QRS and T waves are produced. These changes are the result of varying degrees of ventricular fusion.

Fig. 2 shows the standard leads before and after the ligation of the anterior descending coronary artery at a point midway between the apex and base of the heart. The ligation of this artery produced an anterior myocardial infarction involving the apex of the left ventricle which was grossly evident. Fusion was accomplished an hour after the ligation by premature stimulation of the right ventricle. Inspection of the record reveals that fusion produces rather marked changes in the configuration of the electrocardiogram, but the pattern of acute myocardial infarction with S-T segment changes is partially preserved.

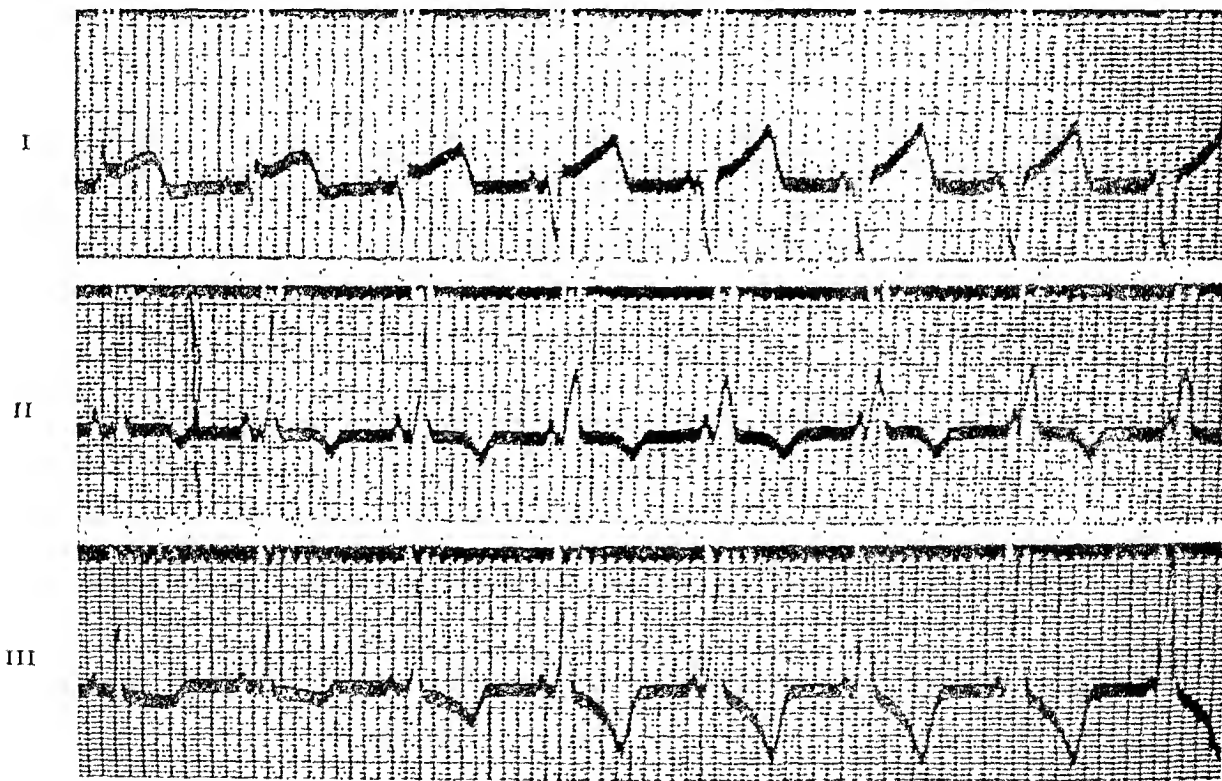


Fig. 3.—Cat No. 5. Variable fusion produced by pre-excitation of the left ventricle after ligation of the anterior coronary artery. The first beat in each lead is a normal complex and shows the acute changes of myocardial infarction. The following beats are fusion beats with a gradual transition to the form of a pure ventricular extrasystole. See Fig. 1 for normal electrocardiogram of same animal.

Fig. 3 shows fusion produced by pre-excitation of the left ventricle after ligation of the anterior coronary artery in the same position. Here the pattern of the myocardial infarction is difficult to recognize in the fusion beats, in contrast to the previous electrocardiogram where pre-excitation of the right ventricle was produced.

DISCUSSION

Inspection of the records reproduced in recent articles of Wolff-Parkinson-White syndrome with myocardial infarction indicates that in no case were there definite clear-cut changes indicative of a large full-thickness infarct with Q-wave and S-T segment changes. Some records showed inversion of the T waves for a period of days or weeks, combined with a clinical history suggestive of acute myocardial infarction. It is known that changes in the character of the T wave may occur in the Wolff-Parkinson-White syndrome which are the result of varying degrees of fusion. Such changes are illustrated in Fig. 4, taken from a human case. The changes in the QRS complex and T waves are seen in all leads, but particularly in Lead III. Such changes in the T wave, due to variable fusion, are very difficult to differentiate from T-wave changes due to underlying myocardial pathology. In addition, Wendkos and Nadler⁶ have recently shown that instability of the T waves, as seen in cases of neurocirculatory asthenia, can occur in patients showing a Wolff-Parkinson-White syndrome.

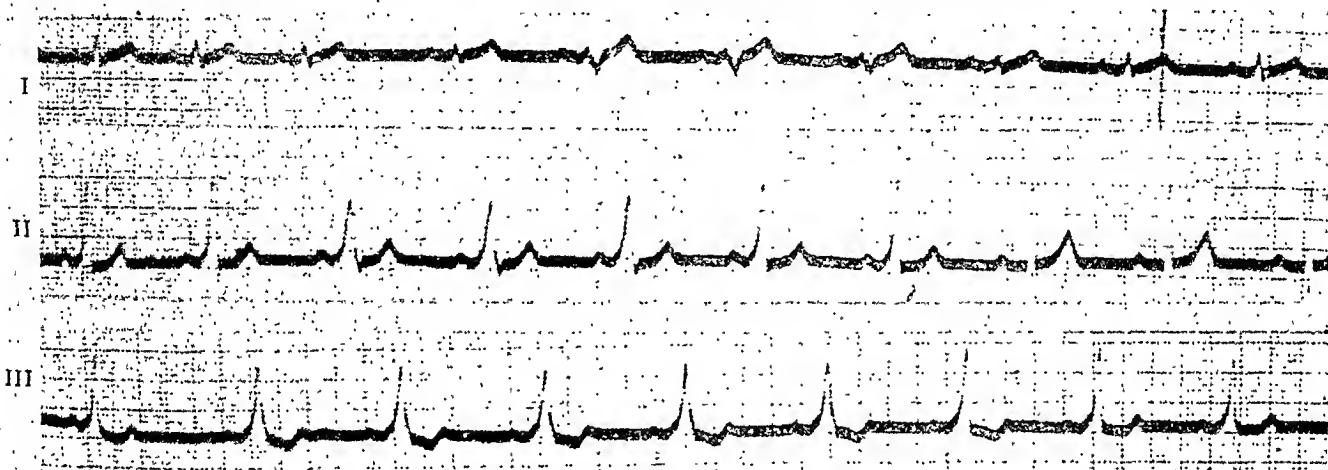


Fig. 4.—A human case showing variable fusion. A few normal complexes can be seen in Leads I and II, but all complexes in Lead III show the Wolff-Parkinson-White syndrome. Variations in the character of the abnormal complexes are apparent.

Our experimental findings indicate that it should be possible to diagnose a large infarct, particularly during the acute stage when changes in the S-T segments are prominent. It seems to us, however, that changes in the T waves alone would be very difficult to evaluate in the presence of a Wolff-Parkinson-White syndrome. This problem is similar to the difficulty encountered in the diagnosis of myocardial infarction in the presence of bundle branch block, especially in left bundle branch block where, at times, it is difficult or impossible to establish the diagnosis of myocardial infarction.

The diagnosis of myocardial infarction in the presence of Wolff-Parkinson-White syndrome would be much more easily established if the syndrome pattern could be abolished. We suggest that in such cases an attempt should be made to convert the Wolff-Parkinson-White pattern to a normal mechanism. In our hands, the use of quinidine⁸ has been satisfactory for this purpose; other measures are, at times, successful.

SUMMARY

An experimental study is reported which indicates that the diagnosis of acute myocardial infarction in the presence of Wolff-Parkinson-White syndrome can usually be established if the infarct is large and particularly if the right ventricle is prematurely stimulated. However, in small infarcts producing only T-wave changes, it is doubtful whether the electrocardiographic findings would be sufficient to establish a definite diagnosis of myocardial infarction. It is suggested that an attempt be made to convert the Wolff-Parkinson-White patterns to a normal conduction mechanism when myocardial infarction is suspected.

The authors wish to acknowledge the able technical assistance of Mr. Clarence E. Peterson.

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CARDIAC VIBRATIONAL INTENSITY AND CARDIAC OUTPUT

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RECENTLY we¹ reported in this JOURNAL a somewhat detailed study of the low-frequency vibrations which accompany each heart beat. It was shown that the major portion of the intensity of such vibrations is contributed by the fundamental (that is, the frequency of the individual beat) and its harmonics up to about the fifteenth. During each heart beat the relative intensities of individual harmonics change in a regular fashion. Harmonic analyses of cardiac vibrations were used to support the hypothesis that the "mean" harmonic of the intensity-frequency distribution, calculated over successive short intervals of the heart cycle, is related in a simple manner to the rate of change in length of ventricular muscle fibers and, therefore, to the rate of change of ventricular volume. By summing these "mean" harmonics, a curve was produced similar to the ventricular volume curve recorded directly by Wiggers.²

Our original study of cardiac vibrations required elaborate apparatus and tedious calculations. Further study has been simplified by construction of an apparatus which we term a "Heart Sound Meter" (H.S.M.), which converts, by electronic means, the complex vibrations picked up at the chest wall into a factor analogous to the "mean" frequency of the intensity-frequency distribution and finally integrates this factor. A record of the output of the heart sound meter, made on such a recording device as the General Electric Photo-Electric Recorder or photographed from the movements of a microammeter in the heart sound meter itself, traces during each heart beat a curve like that of ventricular volume. The coordinates of this curve are time, on the horizontal axis, and a function which we term "resultant frequency" on the vertical axis. (We use the term "resultant frequency" because our apparatus has converted the complex signal of cardiac vibrations picked up at the chest wall into a signal which could be produced at each instant in the heart cycle by presenting a single sine wave signal to the apparatus. The frequency of this simple signal would vary from instant to instant.)

The similarity of the pattern of the heart sound meter output to the ventricular volume curve at once suggested the possibility of using the meter to determine cardiac output. This use is discussed in the present report.

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The most convenient method for determining stroke volume to check heart sound meter records is the ballistocardiograph. In our present study, we used a high-frequency apparatus constructed after the design of Dr. H. A. Blair, of the Department of Physiology, University of Rochester, N. Y.* The oscillations of the bed were converted into electrical energy by a crystal pick-up and recorded on the electrocardiograph channel of the Sanborn Stetho-Cardiette. Stroke volumes were calculated by Starr's³ formula, $S_v = 11 \sqrt{(I + J) C^{3/2} A}$, the amplitude of deflections, I and J , being converted to the sensitivity of Starr's bed by use of the specific constant of our bed and a factor for the sensitivity of the Sanborn Stetho-Cardiette.

COMPARATIVE STUDIES MADE WITH THE HEART SOUND METER AND BALLISTOCARDIOGRAPH

Records made with the ballistocardiograph were compared with heart sound meter records in two ways, which are illustrated by Figs. 1 and 2.

(1) The electrocardiograph and heart sound meter were synchronized, and the heart sound meter output was recorded directly on a General Electric Photo-Electric Recorder. For comparison, a number of successive heart cycles (usually ten) were measured. The records on the Photo-Electric Recorder were adjusted for the slight lack of linearity of the recorder and for the period of the recorder galvanometer.

(2) The heart sound meter data were read from two microammeters, one recording the smoothed "resultant frequency" of some three successive heart cycles and the other showing a function of the "range," that is, the amplitude of each cycle. It was most convenient, in practice, to set this second meter to read the square of the range again smoothed over some three successive beats. While these meters were being read, ballistocardiograph records were made on the Sanborn Stetho-Cardiette and ten successive heart cycles measured to give an average stroke volume.

The general formula for calculation of stroke volume from the heart sound meter is

$$S_v = 2 \Delta f \cdot \bar{f}$$

when Δf is the range and \bar{f} the mean "resultant frequency." This may also be written

$$S_v = f_1^2 - f_2^2$$

where f_1 is the maximum and f_2 the minimum "resultant frequency" in the systolic phase of each heart cycle. This formula is derived from

$$S_v = 2 \Delta f \cdot \bar{f} = 2(f_1 - f_2) \frac{(f_1 + f_2)}{2} = f_1^2 - f_2^2$$

*We wish to thank Dr. W. O. Fenn, Professor of Physiology, University of Rochester, N. Y., for diagrams of the Blair ballistocardiograph.

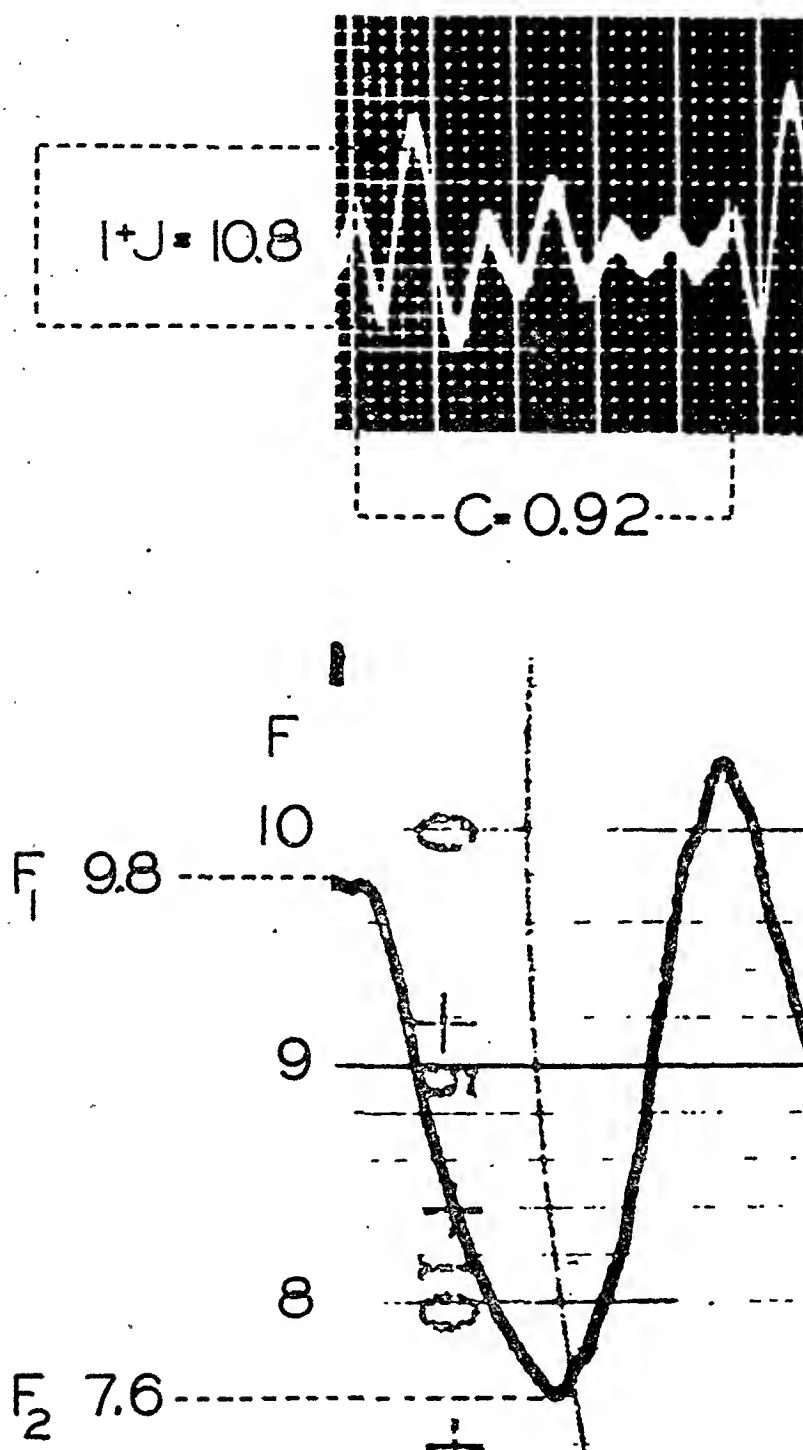


Fig. 1.—Above: Ballistocardiograph record

$$Sv = 11K \sqrt{(I+J)C^{3/2}A} = 53 \text{ c.c.}$$

when

K = constant for bed and recorder sensitivity = 0.988

$A = 2.5$

$C^{3/2} = 0.885$

$(I+J) = 10.8 \text{ mm.}$

Below: Heart sound meter record for same heart beat (made on General Electric Photo-Electric Recorder).

$$Sv = K_1 (f_1^2 - f_2^2) = 52 \text{ c.c.}$$

when

K_1 = constant for recorder galvanometer = 1.35

$f_1 = 9.8 \text{ c.p.s.}$

$f_2 = 7.6 \text{ c.p.s.}$

Stroke Volume During Rest.—The use of the ballistocardiograph as our standard was limited to resting conditions. Records taken immediately after exercise were apt to show abnormal forms. Starr took such forms into consideration by varying his "constant" from 11 to 15, apparently leaving the choice largely to

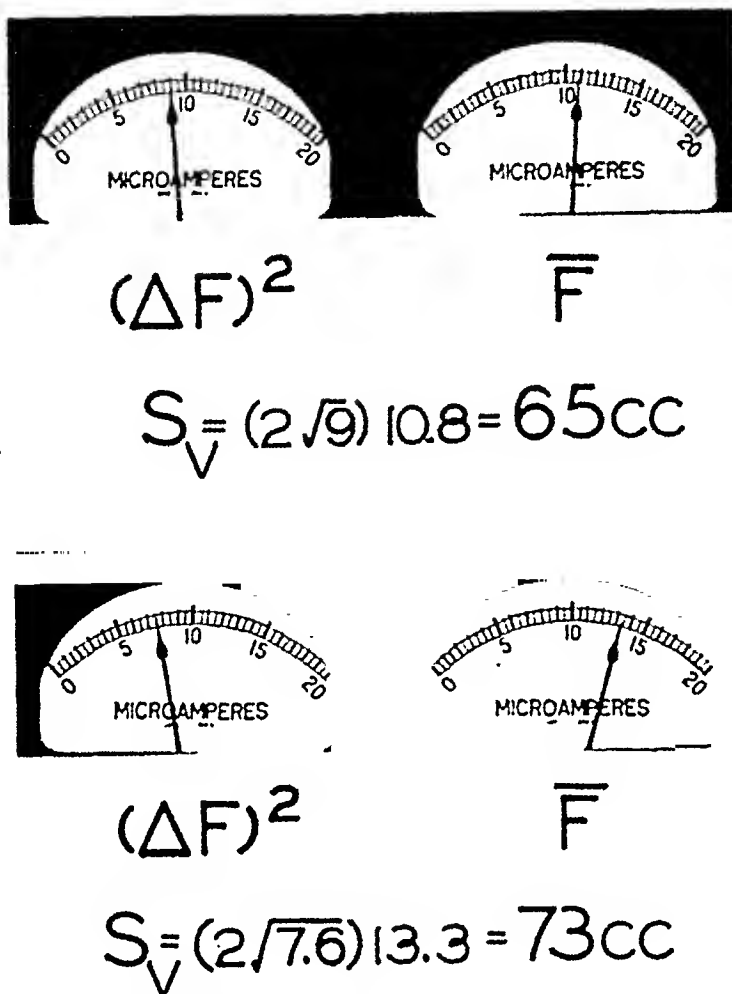


Fig. 2.—Direct calculation of stroke volume from heart sound meter. Left meter records square of range = $(\Delta f)^2$; right meter records mean frequency = \bar{f} . $S_v = 2\Delta f \cdot \bar{f}$. Upper record taken immediately before Master 2-Step exercise test. Lower record taken immediately after exercise test.

the observer. For comparison of two methods of measuring cardiac output, based upon quite different principles, such a procedure appeared of doubtful value, since by simply varying a "constant" one might force the data to a spurious correlation.

Resting stroke volumes measured by the two procedures are plotted in Fig. 3. The limits of variability of the ballistocardiograph record accepted by Starr in comparison with the ethyl-iodide technique, ± 14.3 per cent, are indicated. None of the heart sound meter measurements falls outside this range. The coefficient of correlation between data given by the two methods is 0.95, with a standard error of less than ± 0.02 . Recently, Nickerson, Warren, and

Brannon⁴ have recorded a range of ± 25 per cent in comparing stroke volumes determined by the Fick principle, after right atrial catheterization, with those calculated from the low-frequency ballistocardiograph. They ascribe most of the deviation to unavoidable errors in the Fick technique. Stroke volumes determined by our heart sound meter would appear to be reasonably comparable to those found by other methods, at least under resting conditions.

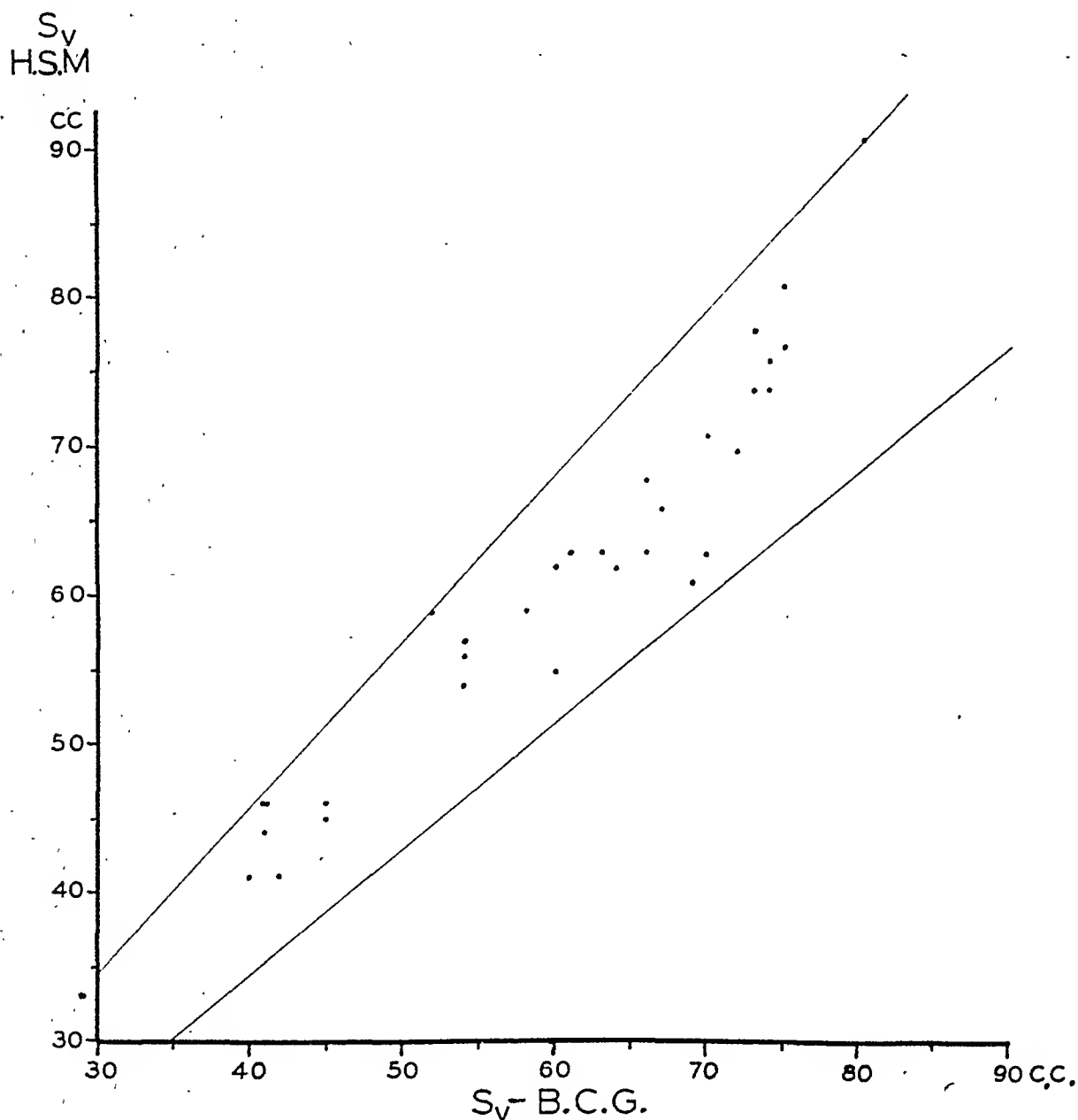


Fig. 3.—Comparison of stroke volumes calculated from ballistocardiograph (B.C.G.) and heart sound meter (H.S.M.). Diagonal lines limit ballistocardiograph ± 14.3 per cent.

Cardiac Output After Moderate Exercise.—To demonstrate the use of the heart sound meter in measuring cardiac output in conditions other than rest when the high-frequency ballistocardiograph might prove unsuitable, we made measurements before and after a series of moderate exercises reported by Grollman⁵ in his classical monograph. Using the acetylene method with a quite elaborate analytical procedure, he was unable to make determinations of stroke

volume as frequently as they can be made with our meter. Table I gives comparative data. Since Grollman does not state how soon after exercise he made his determinations, we have given heart sound meter measurements made immediately (within about twenty seconds) and one or two minutes later. The direction of trend of cardiac output is the same for our tests as for Grollman's.

TABLE I. INFLUENCE OF MILD EXERCISE UPON CARDIAC OUTPUT. COMPARISON OF HEART SOUND METER DATA WITH DATA FROM GROLLMAN⁵

	GROLLMAN	CARDIAC OUTPUT: L./MIN. "HEART SOUND METER" TIME AFTER EXERCISE	C. O.
Resting	4.1	Resting	3.7
Flexing and extending right forearm, once per second	4.8	Immediately 1 minute	4.7 3.7
Flexing right forearm rapidly	6.0	Immediately 2 minutes	5.0 3.6
Alternately flexing and extending both forearms, each and every other second	4.3	Immediately 1 minute	5.1 3.6
Flexing right thigh, once per second	7.7	Immediately 1 minute	6.0 3.8
Alternately flexing both thighs, each every other second	5.0	Immediately 0.5 minute 1 minute	6.3 5.9 3.4

TABLE II. INFLUENCE OF ANOXIA UPON CARDIAC OUTPUT

TIME (MIN.)	EXPERIMENT 1				TIME (MIN.)	EXPERIMENT 2			
		OX- IMETER %	PULSE RATE	C. O. L./MIN.			OX- IMETER %	PULSE RATE	C. O. L./MIN.
0	Resting	98	60	4.44	0	Resting	98	65	5.10
2	Resting	98	60	4.52	3	Resting	98	64	5.41
4	Resting	98	60	4.52	6	Resting	99	66	4.88
6	Resting	98	62	4.56	9	Resting	98	64	4.83
7	Resting	98	60	4.50	11	Nitrogen on	98	64	4.74
8.5	Nitrogen on				13		95	66	4.26
9		99	66	5.39	16	Nitrogen increased	90	78	4.18
11		98	60	4.30	18	Nitrogen increased	85	80	6.14
12.5	Nitrogen increased				21	Nitrogen increased	80*	82*	4.96
15					23		78*	82*	6.10
13.5		95	70	5.38	24		77*	82*	6.61
15		94	68	4.33					
17	Nitrogen increased	91	74	5.48	25		73*	84*	6.21
19		89	76	6.26	26	Nitrogen off			
21	Nitrogen off	86	74	7.30	27		94	66	6.72
23		93	66	5.23	29		96	60	4.49
24		94	62	4.76	30		96	60	4.08
25		95	64	4.66	31		96	56	4.01
27		96	62	4.75					

*Oximeter galvanometer and pulse rate fluctuating widely with respiratory cycle.

Cardiac Output in Anoxia.—The influence of anoxia was studied by allowing our subjects, after a control period, to breathe air into which nitrogen was fed in increasing concentration. Instead of measuring the absolute composition of the air-nitrogen mixture inhaled, we used the Oximeter to indicate the degree of oxygenation of the blood. Table II gives data for two such tests. Fig. 4 is

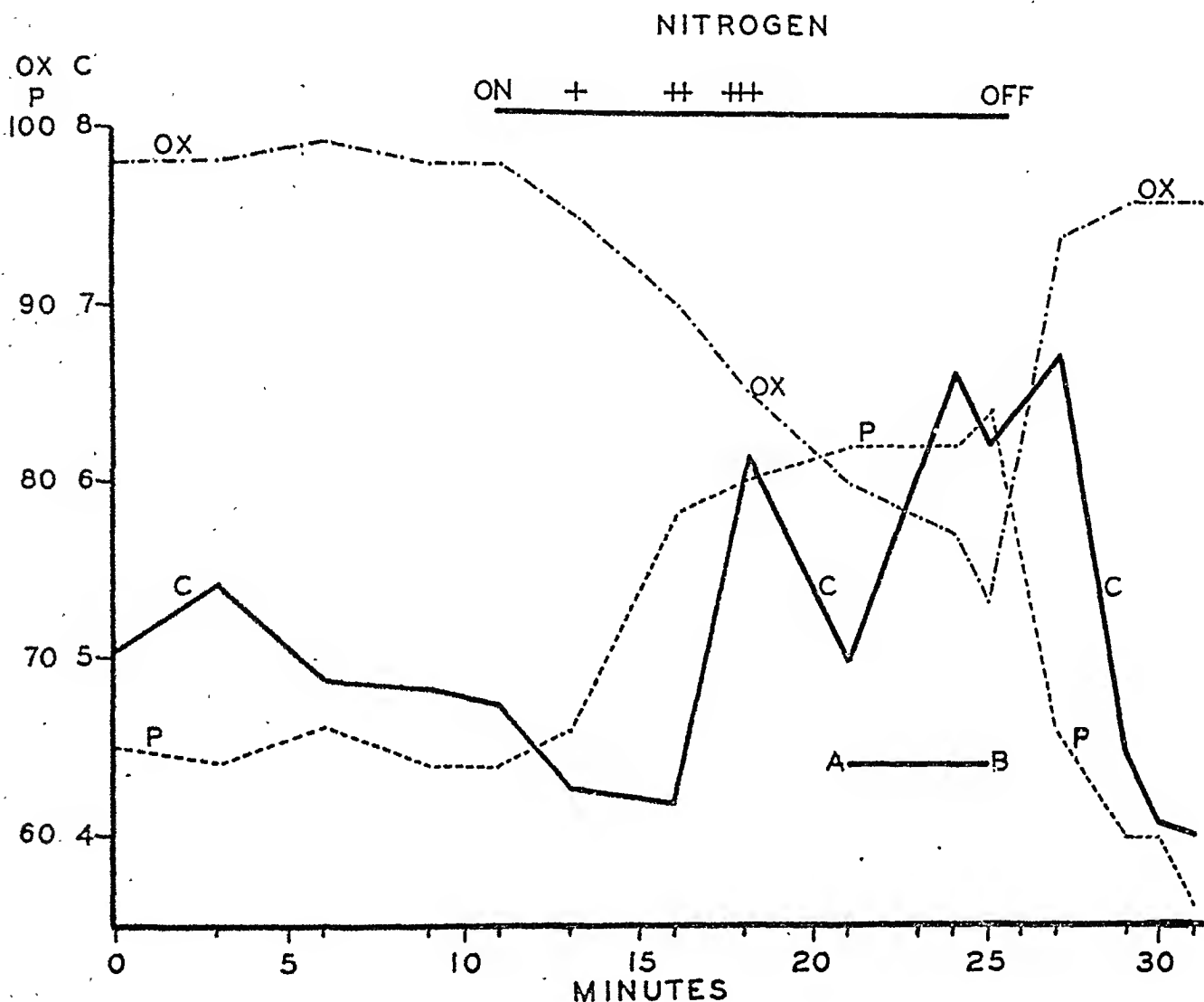


Fig. 4.—Influence of anoxia on cardiac output. Vertical coordinates: C = cardiac output, L./Min.; OX = per cent oxygenation of blood; and P = pulse rate: beats per minute.
 +, ++, +++ indicate increase in nitrogen content of inhaled nitrogen-air mixture.
 A-B. Oximeter and pulse rate fluctuating widely with respiratory cycle.

a plot of the more drastic test (No. 2) in which oxygenation of the blood was reduced almost to 70 per cent. In this experiment, the heart sound meter data were read from the two microammeters already described. It is interesting that greater difficulty was found in counting pulse rate over thirty-second intervals than in reading the heart sound meter. In Experiment 2, between twenty and twenty-five minutes, the patient was breathing irregularly, the Oximeter galvanometer was making wide swings with inhalation and exhalation, and the pulse rate was so irregular that the rates recorded are probably lower than the pulse rates actually attained by the subject.

Grollman reports that in anoxia pulse rate rises before cardiac output and that output should increase when oxygenation of the blood falls to about 83 per cent. Our heart sound meter measurements show pulse rate to rise first, and cardiac output to rise definitely when the blood is about 85 per cent oxygenated.

Reduction of Cardiac Output by Exhaling Against Pressure.—A fall in cardiac output was produced by breathing for seven minutes against an exhalation pressure of 25 cm. of water. Table III shows the trend of cardiac output after the test.

The various procedures used to study measurement of cardiac output by the heart sound meter show that (1) under resting conditions it gives data comparable to that of the high-frequency ballistocardiograph, and (2) under conditions known to change cardiac output, but in which the ballistocardiograph may be unsuitable, the heart sound meter measurements conform in trend to those reported by observers using other methods.

The ease with which a single observer can make frequent measurements, merely reading the two microammeters of the heart sound meter and having few calculations to make, contrasts with the technical difficulties or tedious measurements of other methods and suggests that this new procedure may make possible many studies of cardiac output hitherto found impracticable.

TABLE III. INFLUENCE OF EXHALING AGAINST PRESSURE

	PULSE RATE	STROKE VOLUME C.C.	CARDIAC OUTPUT L./MIN.
Control 1 Resting 10 min.	72	63	4.54
Control 2 Resting 11 min.	71	63	4.47
Exhaling for 7 minutes against 25 cm. water			
20 seconds after test ended	79	37	2.92
90 seconds after test ended	84	56	4.54

SUMMARY

1. An electronic heart sound meter has been devised to convert the complex pattern of low-frequency cardiac vibrations picked up at the chest wall into a simple "resultant frequency."

2. The "resultant frequency" varies during each heart cycle in a manner similar to the ventricular volume curve.

3. Simultaneous records of the high-frequency ballistocardiograph and the heart sound meter made on rested, supine subjects show a close correlation between the cardiac output as calculated by Starr's formula,

$$11 \sqrt{(I + J)C^{3/2}A}$$

and an "output" calculated from the formula,

$$S = f_1^2 - f_2^2$$

in which f_1 is the maximum "resultant frequency" occurring at commencement of systole, and f_2 is the minimum "resultant frequency" at the end of systole.

4. Records of the ballistocardiograph and the heart sound meter taken immediately after exercise do not give comparable calculations of cardiac output. However, heart sound meter data after moderate exercise, after anoxia produced by breathing nitrogen, and after the Flack Test show qualitative and quantitative trends comparable to data obtained by other procedures.

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RESPIRATORY MOVEMENT AS A FACTOR IN THE PRODUCTION OF Q WAVES IN LEAD I AND IN UNIPOLAR LEADS FROM THE LEFT PRECORDIUM IN HUMAN LEFT BUNDLE BRANCH BLOCK

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IN A recent article, Sodeman, Johnston, and Wilson¹ have emphasized the fact that a Q deflection seldom occurs in Lead I in human left bundle branch block. Goldberger² has also commented on this finding. In experimental canine left bundle branch block, on the other hand, a Q deflection frequently occurs in Lead I. This discrepancy could arise in one of two ways: (1) because of a difference in the order of excitation of the different parts of the ventricular muscle in human and in canine left bundle branch block, or (2) because of a difference in the disposition of the heart's surfaces with respect to the thoracic cage and the attachments of the limbs.

Precordial leads in both species, when left bundle branch block is present display such striking similarity in the configuration of the QRS complexes as to make it appear unlikely that there is any important difference in the order of ventricular excitation. This leaves the alternative suggestion of a difference in the position of the heart as the more probable explanation of the observed discrepancy. Some positive evidence may also be adduced in support of this explanation. For example, Foster,⁴ in experiments referred to by Sodeman and co-workers, showed that in dogs in which the left branch of the bundle of His had been severed, a Q wave in Lead I could readily be produced by elevation of the apex, by displacement of the apex to the right, and by rotation of the heart in either direction on its longitudinal axis. When the same experiments were repeated on monkeys with left bundle branch block, the only maneuver by which a Q₁ could be produced was elevation of the apex to 45°, which resulted in a completely negative QS deflection in Lead I. From this and other evidence Sodeman and co-workers concluded that changes in position might readily lead to the production of a Q₁ in a vertically placed heart like the dog's, but were much less likely to do so in a more transversely lying heart like the monkey's or man's.

In further support of this contention, they looked for, but did not find, any peculiarities in the position of the heart in thirteen cases of human left bundle branch block showing a Q₁. In addition to their own thirteen cases, these au-

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thors collected twenty-four others reported in the literature, making thirty-seven in all. Eight of these had come to autopsy. Six of the eight had had myocardial infarction, and in five of these six cases, gross lesions of the interventricular septum were present. Their final conclusion was that a Q wave in Lead I in human left bundle branch block, while not diagnostic, should arouse suspicion that a lesion of the ordinary muscle of the interventricular septum might be present, and they recommend that a full set of precordial leads be taken in such cases "not only for the purpose of ascertaining whether left bundle branch block is really present, but also to find out whether a Q deflection is present in leads from the left side of the precordium and left axilla."

With the septum intact, one would not expect Q deflections to occur in direct unipolar leads from the left ventricular surface in left bundle branch block. When this conduction defect is present the septum is activated entirely from right to left, and the left ventricular cavity is positive in the earliest stage of electrical activity. At this time the muscle of the free wall of the left ventricle has not yet been activated, and it transmits passively the positive cavity potentials to an overlying electrode. The first deflection recorded by the galvanometer must, therefore, be a positive one. Any extensive lesion of the septum, however, may modify these relationships. To quote Sodeman and his co-workers, "If the septum is extensively damaged, the electrical forces produced by its activities are reduced or abolished, and the initial negativity of the right ventricular cavity is transmitted to the left [cavity], and hence to those regions of the left side of the body that are initially positive in left bundle branch block when the septal muscle is healthy. When this happens, Q deflections occur in leads from the left side of the precordium. They may be expected in Lead I also"

REPORT OF A CASE

The following case is reported to show that under certain conditions a Q deflection may be caused to appear and disappear at will in human left bundle branch block, not only in Lead I but also in leads from the left precordium and the left axilla, merely by changes in the position of the heart induced by respiration.

The patient, J. C., was a man 66 years of age, who had been known to have essential hypertension for at least fifteen years. There had never been any chest pain, paroxysmal dyspnea, congestive failure, or other episode suggestive of myocardial infarction. The blood pressure in 1946 was 220/120. X-ray of the chest showed a cardiothoracic ratio of 13.5 to 28.5 and a fairly normal cardiac silhouette. A routine electrocardiogram showed left bundle branch block, and it was observed that not only did the amplitude of the deflections and the electrical axis in the standard limb leads undergo rhythmic variation with the respiratory cycle, but that, in addition, a Q wave appeared in Lead I in inspiration and disappeared in expiration.

To investigate the origin of these Q waves, a full set of unipolar precordial and extremity leads was taken in all phases of respiration. These curves are reproduced in Figs. 1 and 2. During expiration and midrespiration, all leads are entirely characteristic of classical left bundle branch block. The duration of the QRS is 0.14 second; Leads I, V_1 , V_5 , and V_6 all show a monophasic, double-peaked positive deflection with no Q waves. During inspiration, a pronounced and progressive change occurs, marked by a reduction in the amplitude of the bifid R waves and

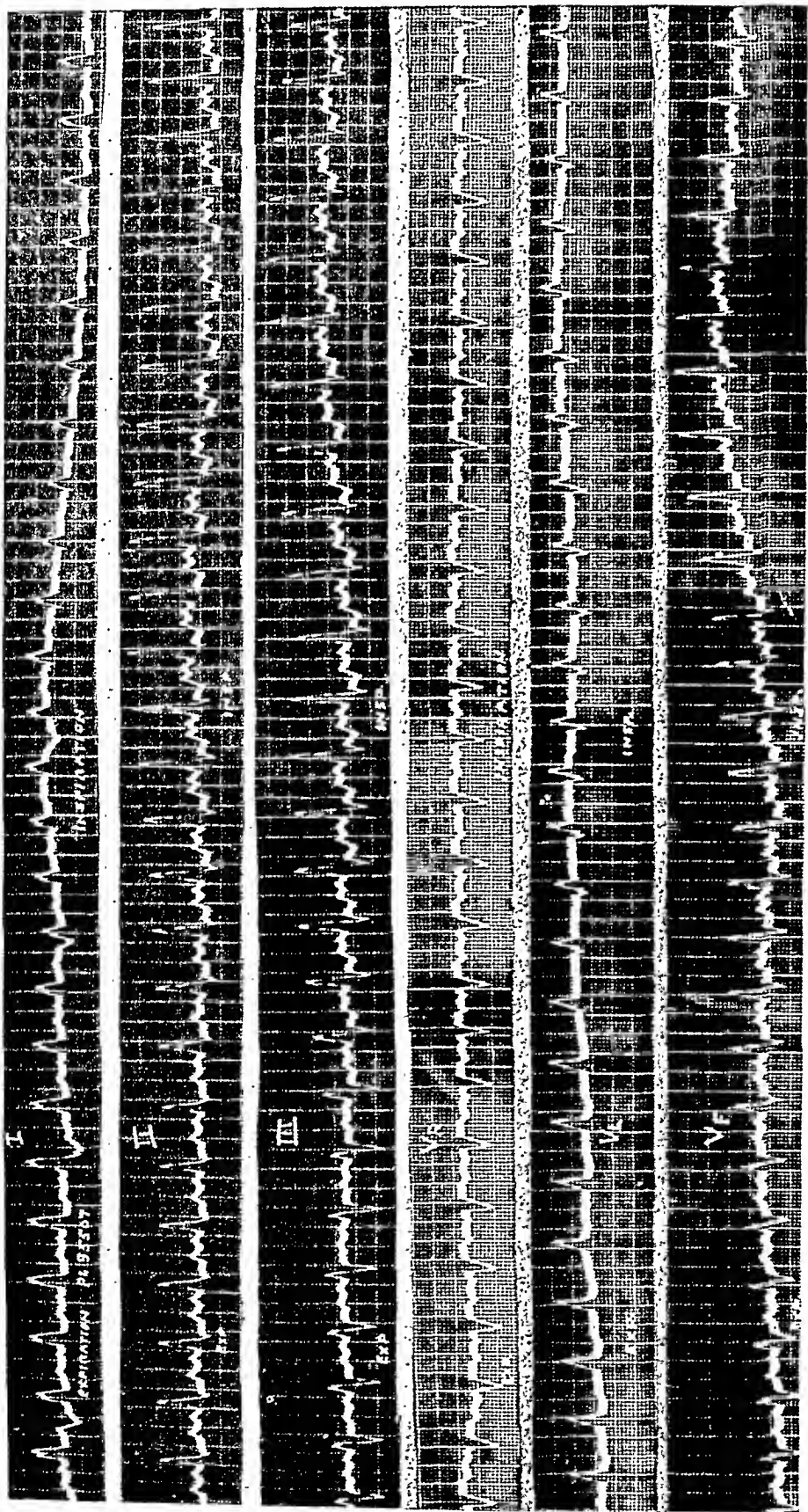


Fig. 1.—Note development of Q waves in Leads I and VL with inspiration.

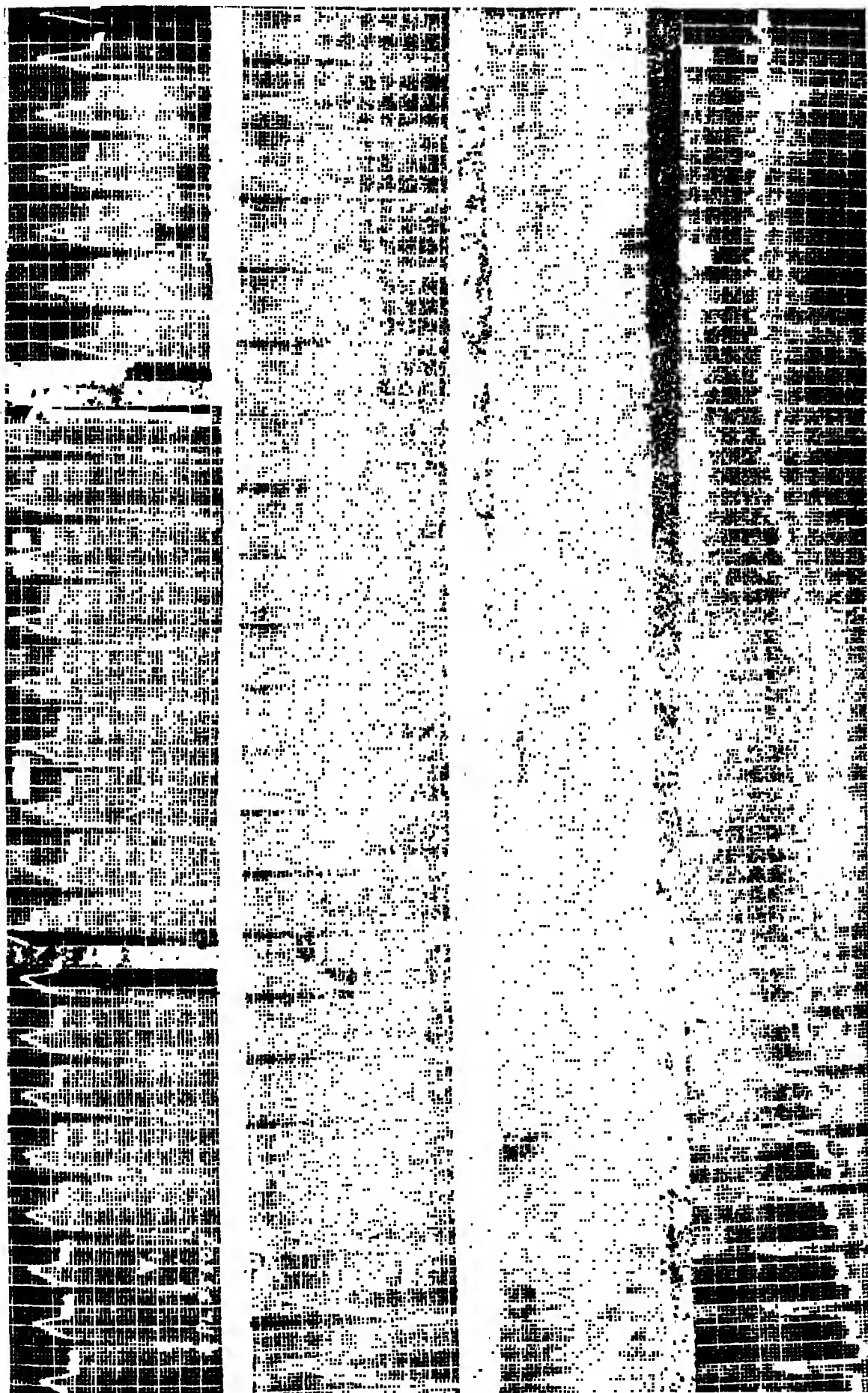


Fig. 2.—Note development of QS waves in Lead V_6 and of Q wave in V_6 with inspiration.

the development of a definite Q wave in Leads I, V_L , and V_6 . In Lead V_6 a more extreme change occurs whereby the main QRS deflection, previously positive, becomes a completely negative QS deflection in deep inspiration. Leads V_R , V_1 , V_2 , and V_3 display little change; they consist of a deep QS deflection throughout the respiratory cycle. Lead V_4 shows a small R wave in expiration. With inspiration this becomes progressively smaller and ultimately disappears so that only a QS deflection remains. In Lead V_F the R wave becomes taller with inspiration and, as might be expected, a similar change occurs in Leads II and III.

DISCUSSION

The striking changes in QRS configuration shown in Figs. 1 and 2 may be considered under three headings: (a) Change in electrical axis; (b) development of Q waves over the left precordium; and (c) development of Q waves in Lead V_L and Lead I.

Change in Electrical Axis.—It is well known that the main electrical axis can be profoundly altered by changes in the position of the heart both when conduction is normal and when bundle branch block is present, and that such changes in position can be brought about by respiratory movements. The effect of deep inspiration is to cause the heart to assume a more vertical position and also to rotate clockwise on its longitudinal axis so as to bring the right ventricle in front of and above the left. This rotation produces modifications in the transmission to the limb attachments of the potential variations derived from the ventricular surfaces, so that the left ventricular potentials tend to be transmitted chiefly to the diaphragm and left leg, while the right ventricular potentials are transmitted to the left axilla. The effect on the electrical axis is a tendency to shift the axis toward the right. Expiration produces the opposite result; the heart assumes a more transverse position and, in addition, undergoes counterclockwise rotation on its longitudinal axis which tends to bring the left ventricle in front of and above the right, with transmission of left ventricular potentials to the left shoulder and right ventricular potentials to the diaphragm and leg. The electrical axis tends to shift to the left. Curves showing right axis deviation in human left bundle branch block associated with a vertical position of the heart have been published by Wilson and associates^{3,6} and by Goldberger.^{2,b} All these curves show a deep S wave in Lead I, but this is preceded in each case by a small R wave, so that no Q wave is present.

Q Deflections in Leads From the Left Precordium.—We have already reviewed the theoretical considerations that lead one to expect that in direct leads from the surface of the left ventricle in left bundle branch block the initial deflection will be positive. Precordial leads resemble the corresponding direct leads very closely as a general rule, but there are certain essential differences which should not be overlooked. A direct unipolar lead is taken from an electrode in actual contact with the epicardial surface; this electrode is influenced almost entirely by the potential variations of the muscle immediately underneath it, and only to a negligible extent by the potential variations of neighboring muscle. In such leads from the left ventricle in experimental uncomplicated left bundle branch block no Q wave has ever been recorded to our knowledge.

In precordial leads, on the other hand, the electrode is not in contact with the ventricular surface, but is separated from it by a considerable layer of tissue that varies with the thickness of the chest wall. Accordingly, these leads do not necessarily record in pure form the potential variations of a limited epicardial area. Wilson and co-workers³ have expressed this relationship as follows: "The potential variations of every element of the epicardial surface contribute in some measure to the potential variations of an electrode placed upon the precordium. But, the magnitude of the contribution made by the potential variations of any given surface element is large if its distance from the electrode is small, and vice versa; it varies roughly as the inverse cube of this distance. For this reason, the potential variations of a precordial electrode are determined to a very large extent by the potential variations of the elements of ventricular surface nearest it. If all or the great majority of these elements simultaneously display potential variations of the same sort, the potential variations of the electrode are of the same character, though much smaller. If, on the other hand, the various elements that are more or less equidistant from the electrode display potential variations of different kinds, the potential variations of the electrode represent a mixture which may not resemble any of its components very closely."

The conditions last described may be produced when an electrode is placed on the precordium over the transitional zone between right and left ventricles. Such an electrode registers a mixture of potentials in which either right or left ventricular influence may predominate as the electrode is moved even slightly toward one side or the other; the same effect is produced if the electrode remains stationary while the heart undergoes rotation, so that the septum moves to right or left of the electrode. In left bundle branch block the complexes derived from right and left ventricles are so distinctive in configuration that even when partially fused, the components contributed by each ventricle remain clearly recognizable.

Fusion of this sort can be seen to occur in Lead V_5 (Fig. 2). During expiration it records in pure form the broad, double-peaked monophasic complex characteristic of leads from the left ventricle in left bundle branch block; there is no Q wave. With the beginning of inspiration the heart is rotated in clockwise fashion on its longitudinal axis, so that the front of the interventricular septum swings to the left. This brings the transition zone closer to the V_5 electrode, and the left ventricular pattern begins to be modified by potentials derived from the right ventricle. The first noticeable effect is the appearance of a tiny notch on the upstroke of the initial R wave. This notch probably represents the small R wave which is present in Lead V_4 in expiration but which disappears in inspiration. As the transition zone swings farther leftward, the potentials derived from the right ventricle begin to dominate those derived from the left: the double positive peaks of the original V_5 complex become lower and lower until finally they appear as mere notches on the descending and ascending limbs of a deep QS deflection representing negative potentials derived from the right ventricle.

Fig. 3 represents a simultaneous recording of Leads V_4 and V_5 at triple camera speed (in expiration, *A*; early inspiration, *B*; and slightly deeper inspiration, *C*) to demonstrate more clearly the time relationships of the various deflections in the two leads. It will be seen that a *Q* wave in Lead V_5 does not appear in Fig. 3, *A* or *B*, but only in *C* after the *R* wave in Lead V_4 has disappeared. Unfortunately, no simultaneous record was obtained in really deep inspiration, but the manner of development of the deep negative deflection in Lead V_5 seen toward the right of Fig. 2 is already clearly indicated.

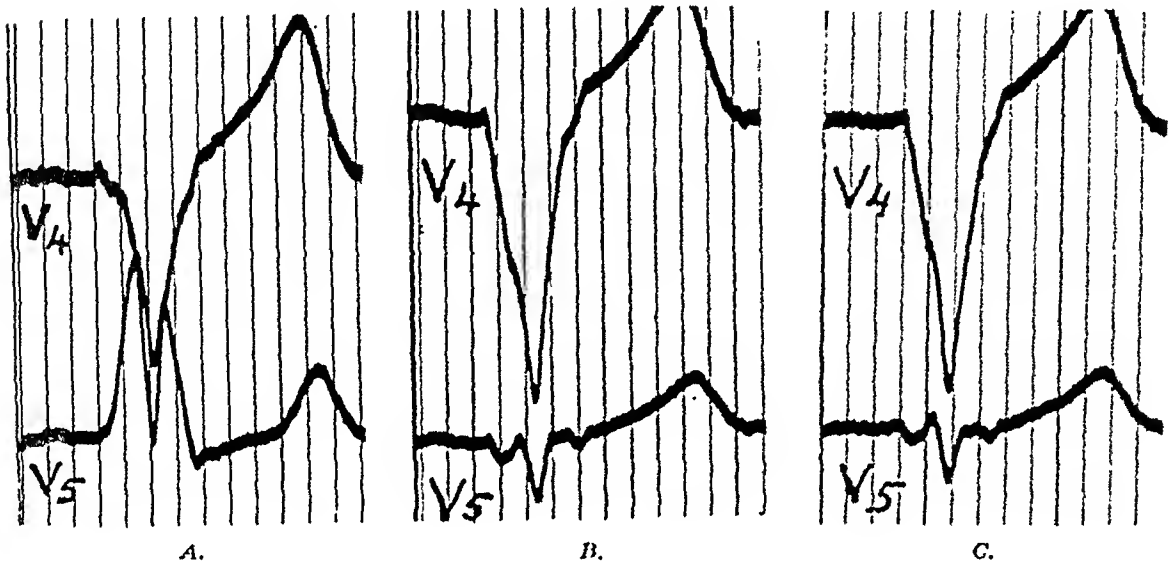


Fig. 3.—Simultaneous recording of Leads V_4 and V_5 (triple camera speed). *A*, expiration; *B*, beginning inspiration; *C*, somewhat deeper inspiration. Note disappearance of *R* in V_4 and coincident appearance of *Q* in V_5 in *C*.

The changes described in Lead V_5 may be seen in modified form in Lead V_6 . Since this electrode is farther from the transition zone than in Lead V_5 , the influence of the right ventricle is less pronounced; but in deep inspiration it is sufficient to produce a marked reduction in the amplitude of the *R* waves and the appearance of a definite *Q* wave, the origin of which is undoubtedly the same as that of the deeper *QS* deflection in Lead V_5 .

In order for a *Q* wave to occur in leads from the left precordium in left bundle branch block as a result of fusion effects such as we have postulated, certain special conditions must be met. Of these, the most important is that there must be no *R* waves in leads from the right precordium. In the present case it is true that Lead V_4 did show a tiny *R* wave, but with inspiration and shift of the septum leftward it rapidly disappeared. It is noteworthy in this connection that left bundle branch block occurs most frequently in hypertensive and arteriosclerotic hearts in which the left ventricle is hypertrophied, a condition which, by itself, may cause suppression of *R* waves over the right precordium.

Q Deflections in Lead I and Lead V_L.—Lead I is a record of the difference in potential from moment to moment at the attachments of the arms: $\text{Lead I} = \text{Lead V}_L - \text{Lead V}_R$. It will be seen in Fig. 1 that V_R showed little or no variation with respiration, maintaining a QS configuration throughout, and, accordingly, any changes occurring in Lead I must be attributed chiefly to potential variations at the left shoulder. Both Lead I and Lead V_L developed a conspicuous Q wave in inspiration. It is entirely likely that the origin of this deflection is the same as that of the Q waves in Leads V₅ and V₆, that is, from potentials transmitted from the right ventricle as the heart rotates with inspiration.

There is, however, another possible explanation for the presence of these Q waves. During inspiration the heart assumes a more vertical position in the thorax and becomes more symmetrically disposed with respect to the two shoulders, so that the left shoulder as well as the right may come to face part of the auricles, great vessels, and valvular orifices at the base of the heart. Its potentials will then represent a mixture of those from the ventricular cavities and those from the lateral aspect of the ventricles. During forced inspiration there may be sufficient clockwise rotation on the heart's long axis to bring the right side of the interventricular septum opposite the left shoulder, in which case activation of the septum from right to left would give rise to initial negativity at the left shoulder. During expiration, the heart resumes its more transverse position and the left shoulder no longer faces into the cavities. Its potentials are now derived chiefly from the lateral aspect of the ventricular surface and are represented by the familiar broad, bifid, positive complexes.

It is probable that the explanation for the common occurrence of a Q₁ in canine left bundle branch lies along these lines. In the dog the heart occupies a very vertical position. Curves published by Wilson and co-workers³ show that when conduction is normal the ventricular complexes in Leads V_R and V_L are very similar, both consisting chiefly of a deep negative deflection, which indicates that both forelimb attachments face the ventricular orifices. In curves from canine left bundle branch block shown in the same article there is a definite Q wave in Lead I, although none appears in leads from the left precordium. These curves show well-marked R waves in leads from the C₁, C₂, C₃, and C₄ positions, so that even at the transition zone there can be no opportunity for the development of Q waves by fusion of complexes derived from right and left ventricles in the manner suggested.

SUMMARY

1. Electrocardiograms are presented which show transient Q waves in Leads I, V_L, V₅, and V₆ in association with left bundle branch block. These Q waves appear and disappear during the respiratory cycle. There is nothing in the patient's history or examination to suggest that he had ever had a myocardial infarct.

2. It is suggested that the Q waves over the left precordium may be produced by fusion of right and left ventricular complexes as the interventricular

septum swings toward the left during inspiration, and that the Q waves in Leads I and V_L probably arise on the same basis. Special conditions that must be present for this to occur are indicated.

3. An alternative explanation is offered with respect to the origin of Q waves in Lead V_L and Lead I, based on the assumption of an unusually vertical position of the heart during inspiration. It is suggested that the more vertical position of the dog's heart is responsible for the frequent occurrence of Q_1 in canine left bundle branch block.

The authors wish to acknowledge the kindness of Dr. Frank N. Wilson in reviewing the manuscript of this paper.

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ELECTROKYMOGRAPHIC STUDIES OF ASYNCHRONISM OF EJECTION FROM THE VENTRICLES

NORMAL SUBJECTS AND PATIENTS WITH BUNDLE BRANCH BLOCK

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THE development of the electrokymograph¹⁻³ provides a new method for studying the motions of the borders of the heart and great vessels in man. With this instrument, records can be obtained of the movements of these borders which accompany ejection of blood from the ventricles. The time relationships of the events recorded from the pulmonary artery and the right ventricle can be compared with those from the ascending aorta and left ventricle. Thus, synchronism or asynchronism of the ejection phases of the two sides of the heart can be determined.

Earlier studies, utilizing the myocardiograph^{4,5} or solenoid recorder,⁶ indicated that contraction of the ventricles could be asynchronous in normal animals. Asynchronism was also demonstrated after cutting a branch of the bundle of His. Katz,⁷ in 1925, recorded intraventricular and intra-arterial pressures in normal dogs and conclusively showed that ejection of blood from the ventricles was not simultaneous in most instances.

The principal methods of studying this problem which have been applied to man include the analysis of (1) the carotid sphygmogram with simultaneously recorded standard lead electrocardiogram, (2) the roentgenkymogram of the pulmonary artery and ascending aorta, (3) the roentgenkymogram with electrocardiogram, (4) the stethogram, carotid sphygmogram, and electrocardiogram, and (5) the right and left "part-electrocardiogram" and stethogram.⁸⁻¹² Despite questions raised as to the reliability of some of these methods for accurately timing cardiovascular phenomena, results generally indicated that asynchronism of ejection occurred, commonly in normal subjects and usually in patients with electrocardiographic evidence of bundle branch block.

This paper is a report on the application of the electrokymograph to the study of ventricular asynchronism.

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METHOD

The motion of the border of the pulmonary artery segment of the cardiovascular silhouette and that of the ascending aorta close to its point of origin were recorded consecutively. These electrokymograms (E.K.Y.) closely resemble the carotid sphygmogram which was recorded simultaneously with each. The time interval from the onset of ejection on the pulmonary artery electrokymogram to the onset of ejection on the carotid sphygmogram was measured and was designated PAc. In the same way, the time interval from the onset of ejection

SCHEMATIC FOR DETERMINING DEGREE OF ASYNCHRONISM

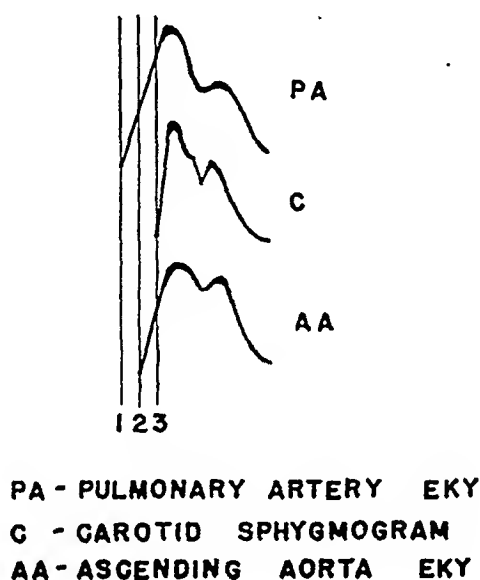


Fig. 1.—Diagrammatic sketch illustrating principles of method. Vertical time lines 1, 2, 3 mark onset of ejection wave on pulmonary artery (PA), ascending aorta (AA), and carotid artery (C), respectively.

1 to 3 = PAc

2 to 3 = AAac

1 to 2 = PAc to AAac difference, a measure of relative time of ejection into these two vessels.

In practice, the records of pulmonary and ascending aorta motion are separately recorded (Fig. 2) in each case simultaneously with the carotid sphygmogram.

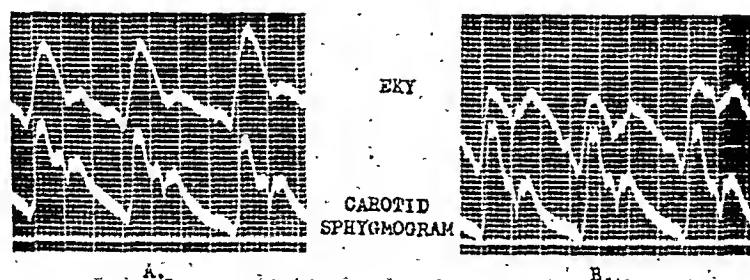


Fig. 2.—Normal electrokymograms representing motion of borders of pulmonary artery (A) and ascending aorta (B). Lower tracing in each case is carotid sphygmogram. Time and amplitude markings same as in electrocardiogram. PAc = 0.02 second and AAac = 0.02 second, indicating simultaneous ejection of blood from ventricles.

on the ascending aorta electrokymogram to the onset of ejection on the carotid sphygmogram was measured and was designated AAc. The carotid sphygmogram thus served as a common point of reference for determining the time interval between the onset of ejection on the pulmonary artery and the ascending aorta electrokymograms (Figs. 1 and 2). For example, in Fig. 2 the time difference between ejection on the pulmonary artery and the carotid artery curves was 0.02 second, and the ascending aorta to carotid time difference was 0.02 second. When, as in this case, PAc and AAc are equal, the interpretation was that these vessels received blood simultaneously and both ventricles ejected blood simultaneously (Table I, Subjects 22 through 35). When the pulmonary artery to

TABLE I. DATA ON NORMAL VENTRICULAR ASYNCHRONISM (SIXTY-EIGHT ADULTS, 17 TO 32 YEARS OF AGE, WITHOUT CARDIOVASCULAR DISEASE)

PATIENT NO.	PAc	AAc	PAc to AAc DIFFERENCE*	LEADING VENTRICLE	PATIENT NO.	PAc	AAc	PAc to AAc DIFFERENCE*	LEADING VENTRICLE
1	.03	.00	.03	Right	35	.01	.01	.00	Even
2	.03	.00	.03	Right	36	.00	.01	-.01	Left
3	.03	.01	.02	Right	37	.02	.03	-.01	Left
4	.03	.01	.02	Right	38	.01	.02	-.01	Left
5	.03	.01	.02	Right	39	.01	.02	-.01	Left
6	.03	.01	.02	Right	40	.01	.02	-.01	Left
7	.03	.01	.02	Right	41	.00	.01	-.01	Left
8	.03	.01	.02	Right	42	.00	.01	-.01	Left
9	.01	.00	.01	Right	43	.01	.02	-.01	Left
10	.02	.01	.01	Right	44	.00	.01	-.01	Left
11	.01	.00	.01	Right	45	.02	.03	-.01	Left
12	.01	.00	.01	Right	46	-.01	.00	-.01	Left
13	.03	.02	.01	Right	47	.00	.01	-.01	Left
14	.01	.00	.01	Right	48	.01	.02	-.01	Left
15	.03	.02	.01	Right	49	.00	.01	-.01	Left
16	.02	.01	.01	Right	50	.02	.03	-.01	Left
17	.02	.01	.01	Right	51	.00	.01	-.01	Left
18	.02	.01	.01	Right	52	.01	.02	-.01	Left
19	.02	.01	.01	Right	53	.01	.02	-.01	Left
20	.02	.01	.01	Right	54	.01	.02	-.01	Left
21	.03	.02	.01	Right	55	-.01	.01	-.02	Left
22	.01	.01	.00	Even	56	.01	.03	-.02	Left
23	.01	.01	.00	Even	57	-.01	.01	-.02	Left
24	.02	.02	.00	Even	58	-.01	.01	-.02	Left
25	.01	.01	.00	Even	59	-.01	.01	-.02	Left
26	.01	.01	.00	Even	60	-.01	.01	-.02	Left
27	.03	.03	.00	Even	61	-.01	.01	-.02	Left
28	.02	.02	.00	Even	62	-.01	.01	-.02	Left
29	.01	.01	.00	Even	63	-.01	.01	-.02	Left
30	.00	.00	.00	Even	64	.00	.02	-.02	Left
31	.03	.03	.00	Even	65	-.01	.01	-.02	Left
32	.00	.00	.00	Even	66	-.01	.02	-.03	Left
33	.02	.02	.00	Even	67	-.01	.02	-.03	Left
34	.02	.02	.00	Even	68	-.01	.02	-.03	Left

PAc = Interval from ejection on pulmonary artery E.K.Y. to ejection on carotid sphygmogram. Plus value means pulmonary artery ejection precedes carotid ejection. Minus (—) value means pulmonary artery ejection follows carotid ejection.

AAc = Interval from ejection on ascending aorta E.K.Y. to ejection on carotid sphygmogram. All times in seconds.

*Plus value means pulmonary artery ejection precedes ascending aorta ejection. Minus (—) value means pulmonary artery ejection follows ascending aorta ejection.

carotid time (PAC) was longer than the ascending aorta to carotid time (AAc) the interpretation was that the right ventricle ejected its blood first (Subjects 1 through 21). When AAc was longer than PAC the interpretation was that the left ventricle ejected its blood first (Subjects 36 through 68).

Wolferth and Margolies⁸ and Hirsch and Gubner⁹ used the roentgenkymograms of aortic and pulmonary arterial waves for studying asynchronism in the ejection phases of the two ventricles. The method proposed herein differs only in the manner in which the records are obtained and timing is determined.

The electrokymogram is an electrical and instantaneous recording, while the carotid sphygmogram is recorded by an air conduction system. We have measured the lag in this latter system and it is consistently 0.01 second for the six feet of tubing we utilize. This correction factor was applied to all the time measurements.

The use of the carotid sphygmogram as a common time-reference curve is considered valid as long as no significant cardiodynamic changes occur between the time the ascending aorta and pulmonary artery records are obtained. The great vessel records were taken within two or three minutes of one another with the patient standing in a relaxed position. Preliminary observations indicated that the time relationships between the onset of ejection on the pulmonary artery, ascending aorta, and carotid curves do not vary significantly under these conditions. Measurements were the same whether right or left carotid sphygmograms were used.

The records are obtained at comparable points on the ascending aorta and pulmonary artery close to the respective semilunar valves. Some variations will occur in selecting the points of recording. The errors introduced by this and by differences in pulse wave transmission times in the two vessels are less than the 0.01 second error inherent in the method and, therefore, insignificant.

The sixty-eight normal subjects were medical students and nurses, 17 to 32 years of age, with no evidence of cardiovascular disease. The sixteen subjects with intraventricular block had standard and precordial electrocardiograms taken. In all cases, two qualified examiners agreed as to the electrocardiographic diagnosis.

RESULTS

In Normal Subjects.—Table I shows the results of measurements of asynchronism in the normal adults studied. Asynchronism of ejection occurred in fifty-four of sixty-eight subjects. Left ventricular ejection led by 0.01 to 0.03 second in thirty-three cases; right ventricular ejection led by 0.01 to 0.03 second in twenty-one cases; and ejection appeared synchronous in fourteen cases. These results are strikingly similar to those obtained by Katz⁷ in his work with dogs, both as to the degree of asynchronism and as to the order of ventricular ejection.

These measurements were obtained on young adults. In older subjects, more rapid transmission of the pulse wave might be expected, possibly altering measurements and relationships. However, in a small group of older adults no significant variations were noted in the PAC and AAc measurements.

It is of interest to note in Table I that the PAc interval normally varies within a narrow range (+0.03 to -0.01 second). Ejection on the pulmonary artery may follow that on the carotid artery ($\text{PAc} = -0.01$ second) when the left ventricle ejects its blood sufficiently in advance of the right ventricle.¹³ It should be noted also that the PAc interval alone does not measure the exact degree of ventricular asynchronism or indicate which ventricle ejects its blood first. To determine this from the PAc measurement, it would be necessary to take into account (1) the difference in speed of pulse wave transmission, and (2) the difference in distance from the ventricles to the points of recording on the pulmonary and carotid arteries.

Measurements of ascending aorta to carotid transmission time varied from 0.00 to 0.03 second. A transmission time of 0.01 to 0.02 second closely agrees with previous estimates, but times of 0.03 and particularly of 0.00 would seem erroneous. There are two possible explanations for this: (1) The measurements are probably accurate only to within 0.01 second, and (2) it is known that positional changes can occur on the ascending aorta during isometric contraction of the ventricles. If this positional change results in lateral motion of the vessel border, it will occur just prior to and may merge with the lateral movement as a result of ejection of blood. What appeared to be the onset of the ejection wave might actually be the onset of the positional change and thus give an apparently prolonged AAc time. If, on the other hand, the positional change results in medial motion of the vessel border, it may offset the beginning of lateral motion resulting from ejection and delay the upstroke of the ejection wave. In most cases, it is possible to distinguish these positional changes when they occur. More detailed study of the pulse wave transmission times as measured by the electrokymograph will be the subject of a separate report.

In view of these sources of error, it is probable that when readings of 0.00 and 0.03 second were obtained, the true values were closer to 0.01 and 0.02 second, respectively. When the PAc to AAc difference was recalculated after these latter values were arbitrarily assumed for the AAc time, the findings differed very little from those of Table I. The number of subjects showing the left ventricle leading became thirty-two (thirty-three in Table I); cases showing synchronous ejection became seventeen (fourteen in Table I); cases showing the right ventricle in the lead became nineteen (twenty-one in Table I).

In Patients With Intraventricular Block.—The same method of study was applied to a group of sixteen patients with clear-cut electrocardiographic signs of left or right bundle branch block. (No cases of unclassified or indeterminate block were encountered.) It was immediately apparent that the PAc time was significantly altered as compared with that of the normal subjects. In 100 normal young adults, ejection on the pulmonary artery occurred from 0.03 second before to 0.01 second after ejection on the carotid artery (that is, $\text{PAc} = 0.03$ to -0.01 second). As shown in Table II, in fifteen of our subjects with bundle branch block, this PAc measurement fell outside the normal range. It measured more than 0.03 second in nine of ten patients with left bundle branch block and less than -0.01 second in each of six patients with right bundle branch block.

(examples shown in Figs. 3, 4, and 5). These findings suggested that the measurement of the PAc interval alone might be adequate to detect bundle branch block. Before this was accepted as a valid single criterion, other possible criteria were studied.

TABLE II. RESULTS OF ASYNCHRONISM STUDIES IN BUNDLE BRANCH BLOCK

DIAGNOSIS BY ECG	PAC IN SECONDS	INTERPRETATION*
Right bundle branch block		
W. F.	-.05	Definite bundle branch block
E. H.	-.05	Definite bundle branch block
W. K.	-.05	Definite bundle branch block
L. M.	-.05	Definite bundle branch block
E. M.	-.04	Definite bundle branch block
B. Y.	-.04	Definite bundle branch block
Left bundle branch block		
W. C.	+.07	Definite bundle branch block
J. K.	+.07	Definite bundle branch block
H. S.	+.07	Definite bundle branch block
M. H.	+.07	Definite bundle branch block
B. L.	+.06	Definite bundle branch block
J. Z.	+.06	Definite bundle branch block
Be. L.	+.05	Definite bundle branch block
H. A.	+.04	Borderline bundle branch block
R. M.	+.04	Borderline bundle branch block
C. J.	+.03	Normal

*Note: "Normal" = PAc \pm 0.03 to -0.01 second; "borderline" = PAc within 0.01 second of "normal"; "definite" = PAc more than 0.01 second outside "normal."

At the time these patients were examined, both the electrokymograph and the technique of its use were in a developmental stage and we obtained satisfactory records of the motions of the ascending aorta in only five of the sixteen patients. In them it was possible to determine the degree of ventricular asynchronism by comparing PAc and AAc measurements, as was done with the normal subjects. These five were individuals with left bundle branch block. Their PAc to AAc difference measured 0.07, 0.06, 0.05, 0.04, and 0.03 second, respectively (upper limit of normal, 0.03 second). Thus, in all but one case, the degree of ventricular asynchronism was abnormally increased and the lag in left ventricular ejection was greater than in normal subjects. The same conclusion was reached from analysis of the PAc measurement alone in all but one patient (B. L.). In this patient, the PAc measurement (0.06 second) indicated a distinct left bundle branch block, while the PAc to AAc difference gave a reading of 0.03 second, which is within the normal variation.

There were twelve among the group of sixteen patients with intraventricular block in whom we failed to obtain satisfactory records of the ascending aorta but had good electrokymographs of the aortic knob. This information was used to calculate the time of ejection into the ascending aorta. The time for transmission of the pulse wave from the ascending aorta to the aortic knob was found to average 0.014 second (0.00 to 0.03 second) by electrokymographic

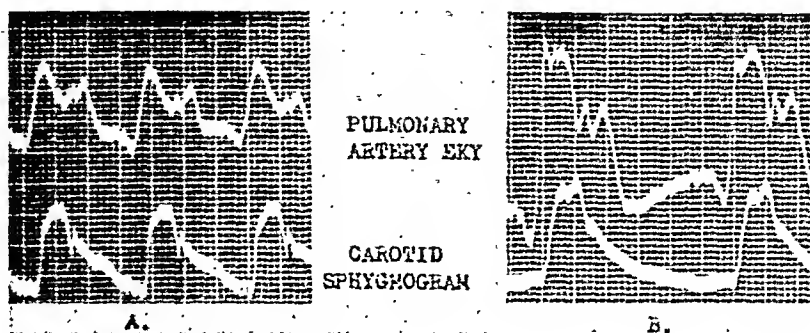


Fig. 3.—Electrocardiogram illustrating left bundle branch block. A, B. L., 52 years of age, man. Electrocardiogram shows left bundle branch block (QRS, 0.14 second), $P_{Ac} = 0.07$ second. B, H. S., 39 years of age, man. Electrocardiogram shows left bundle branch block with A-V dissociation (QRS, 0.14 second), $P_{Ac} = 0.08$ second.

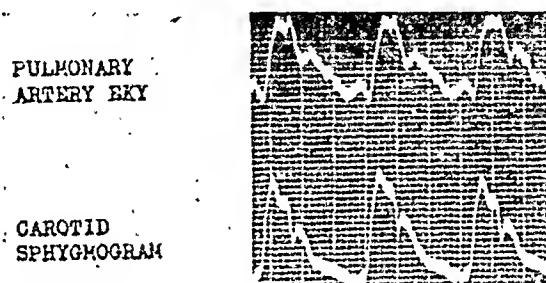


Fig. 4.—Electrocardiogram illustrating right bundle branch block. E. M., 42-year-old man. Electrocardiogram shows right bundle branch block (QRS, 0.14 second). $P_{Ac} = -0.03$ second.

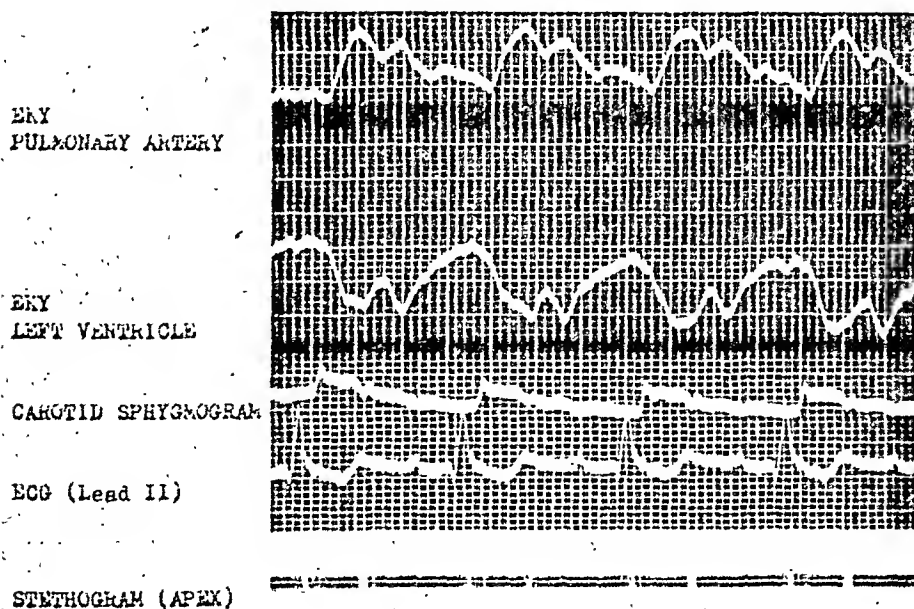


Fig. 5.—Example of right bundle branch block and simultaneous recording of multiple events. Lead II of electrocardiogram shown. Standard and precordial leads show right bundle branch block (QRS, 0.15 second), $P_{Ac} = -0.05$ second.

study. By applying this correction factor to the AKc time (ejection on the aortic knob electrokymogram to ejection on the carotid syphgmogram), we obtained an estimated AAc interval for each of these twelve cases. With this method, the PAc to AAc difference was outside normal limits, varying from 0.04 to 0.07 second, in eleven patients; while in one, B. L., it measured 0.03 second, the upper limit of normal. Wolferth and associates¹³ compared the onset of ejection on the aortic knob and pulmonary artery segments of the roentgenkymograms of patients with left bundle branch block. By allowing 0.01 second for transmission from the ascending aorta to the aortic knob, they were able to calculate the difference between the time of ejection on the ascending aorta and pulmonary artery. This difference varied from 0.04 to 0.07 second in patients with left bundle branch block, agreeing with our results.

All these cross correlations of the PAc, AAc, and AKc times gave results in excellent agreement with those we obtained from analyzing the PAc time alone. It appears, therefore, that the simpler determination of the pulmonary artery to carotid time alone will detect abnormal degrees of ventricular asynchronism.

COMMENTS

The results obtained by these studies of normal man closely correspond with those found by Katz⁷ in his study of dogs. In twenty-four experiments he found that right ventricular ejection preceded in eleven instances by 0.016 to 0.027 second; left ventricular ejection preceded in eleven instances by 0.013 to 0.03 second; ejection from the two ventricles was simultaneous in two cases. In both his and our studies, asynchronous ejection occurred more commonly than synchronous ejection: either the right or left ventricle led in about the same percentage of cases. Our findings were also in accord with those of Katz in regard to the degree of asynchronism observed.

With the electrokymograph the motion of the right and left ventricular borders can be recorded. The most direct method for studying contraction and ejection phenomena would be to record these simultaneously and make a direct comparison of activities. However, the technique of simultaneously recording motion of the two ventricles is difficult and requires special apparatus. The records obtained so far have not shown sharply defined and measurable points of ejection.

Another approach is to record simultaneously electrokymograms of the pulmonary artery and the ascending aorta. We have not been able to do this in a group of normal young people because the anatomic position of these two vessels was such that they could not both be brought into silhouette at the same time. In one of three attempts with older individuals with bundle branch block, we obtained satisfactory simultaneous recordings of these two great vessels. This record indicated a left bundle branch block of the same degree as found by analysis of the single electrokymogram of the pulmonary artery and the carotid sphygmogram.

It is simpler and quicker to analyze the pulmonary artery electrokymogram than to use the more complex methods. The measurement of the PAc interval alone appears adequate for detecting increased degrees of asynchronism in patients with intraventricular block.

SUMMARY

1. The electrokymograph was utilized to study asynchronism of ejection from the ventricles of man.

2. Analysis of electrokymograms from the pulmonary artery and the ascending aorta demonstrated that asynchronous ventricular ejection was more frequent than synchronous ejection in the normal subjects studied.

3. A simple method of detecting increased degrees of asynchronism in patients with bundle branch block was demonstrated, utilizing the pulmonary artery electrokymograms and the simultaneously recorded carotid sphygmogram.

4. In patients with left bundle branch block, the ejection wave on the pulmonary artery curve preceded that on the carotid record by a significantly greater time than in the normal subjects.

5. In patients with right bundle branch block, the ejection wave on the pulmonary artery curve occurred after that on the carotid record by a significantly greater time than in the normal subjects.

Electrocardiograms were interpreted by Doctor Hugo Roesler, who gave invaluable encouragement and aid in this study.

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ON THE EVIDENCE FOR GENERALIZED ARTERIOLAR CONSTRICTION IN COARCTATION OF THE AORTA

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IN 1938, Steele and Cohn,¹ and in 1941, Steele² advanced the opinion that the hypertension which is present in the arms in most cases of coarctation of the aorta is not solely due to the direct mechanical effects of the lesion, but rather that it is due to the occurrence of increased arteriolar tone throughout the body. The significance of experiments with acute obstruction of the aorta performed by Brothner,³ which he interpreted as supporting the opinion expressed earlier by Blumgart, Lawrence, and Ernstene⁴ (who believed that the hypertension is of purely mechanical causation), has been discounted by Steele.²

The opinion that widespread arteriolar constriction exists is based on two pieces of evidence. The first is the finding of Prinzmetal and Wilson⁵ and of Pickering,⁶ who independently noted that in cases of coarctation the resting volume of blood flow through the hand and forearm, as estimated by a plethysmographic method, was not increased above the normal. This finding is interpreted as evidence for the existence of arteriolar constriction in the upper portion of the body. The second is the observation of Steele and Cohn,¹ and of Steele,² that in two of three cases of coarctation of the aorta, diastolic pressure in the femoral artery, measured directly, was increased above normal levels. This observation was interpreted by Steele² as evidence of general increase in arteriolar tone throughout the body.

The observations of Prinzmetal and Wilson and those of Pickering do not, however, afford positive proof of the existence of arteriolar constriction in the upper portion of the body in coarctation of the aorta; a body of purely clinical evidence suggests strongly that, at least in some cases, blood flow is increased through tissues supplied by arteries which take origin above the constricted isthmus, and decreased in the regions supplied by arteries which arise below the obstruction. In this body of evidence, which has recently been summarized by Reifenshtein and associates,⁷ may be mentioned warm hands and cold feet, high facial coloring,⁸ numbness and pallor of the feet and legs, overdevelopment of the upper as compared with the lower extremities, and intermittent claudication.⁴ The occurrence of a capillary pulse in the lips⁸ is also strong but not incontrovertible evidence against the existence of arteriolar constriction in this region.

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It should be noted, also, that if *uniform* arteriolar constriction throughout the body exists in coarctation of the aorta, the flow of blood through the upper portion of the body should be increased and that through the lower portion decreased, just the same as if arteriolar tone throughout the body were normal. If flow is not increased in the tissues which receive blood from the aorta above the constricted isthmus, it must follow that flow in the tissues which receive blood from arteries which arise below the isthmus is not decreased, and therefore, that *selective* constriction of the arterioles in the upper portion of the body exists.

With regard to the significance of the second piece of evidence, elevation of the diastolic pressure in the femoral artery cannot, per se, be interpreted as evidence for a general increase in arteriolar tone throughout the body. The pressure in a given peripheral artery furnishes an accurate index of peripheral resistance throughout the body (in relation to cardiac output and the capacity of the arterial tree) only if no abnormal resistance intervenes between the heart and this artery to oppose the flow of blood or to interfere with the transmission of pressure waves.

Further, the cardiac output, the capacity of the arterial system, and the magnitude of the factors which oppose the flow of blood determine *mean* pressure in the aorta; no one of them determines the level of diastolic pressure. Systolic pressure, diastolic pressure, and all other instantaneous pressures depend upon the mean pressure and upon the amplitude and form of the aortic pressure pulse. Obviously, if the pulse is of large amplitude, the values for systolic, mean, and diastolic pressure are widely separated, while if the amplitude of the pulse is small, these values all lie close together. Thus, it is quite possible, if the pressure pulse is of abnormally small amplitude, for the diastolic pressure to be elevated even though mean pressure is decreased. Normally, mean intra-aortic pressure is about 105 mm. Hg; systolic pressure, 130; diastolic, 85; and pulse pressure, 45. Should factors intervene to reduce mean pressure to 98 and pulse pressure to 10, systolic pressure might then be 103, and diastolic, 93.

In coarctation of the aorta, an abnormal resistance to the flow of blood and to the transmission of pressure waves is interposed between the upper and lower segments of the aorta. For reasons that are quite clear, this resistance causes elevation of mean pressure in the proximal segment and increase in the amplitude of its pressure pulse. These changes are reflected in the pressures in the brachial artery. For the same reasons, mean pressure in the distal portion is lower than that in the proximal segment, and the pressure pulse in the distal aorta is markedly decreased in amplitude. These changes are reflected in the pressures in the femoral artery.

In the brachial artery, diastolic pressure is considerably removed from mean pressure, while in the femoral artery diastolic pressure is much nearer the mean. For this reason, it should be expected that diastolic pressure in the femoral artery might well be as high as or higher than diastolic pressure in the brachial

artery; this is especially likely to be the case if mean pressure in the distal aorta is not greatly below that in the proximal segment.

Other examples of elevation of the diastolic pressure as a result solely of decrease in the amplitude of the pulse wave may be cited.

1. In instances of partial obstruction of one subclavian artery by pressure of an aortic aneurysm or due to sclerotic change, diastolic pressure in the brachial artery of the obstructed side is often higher than that in the opposite arm. In a patient recently seen by the writer, there was partial obstruction of the right subclavian artery. The pulse at the left wrist was of normal volume; that at the right, very small. Arterial pressure in the left arm was 140/90; in the right, 115/105. The elevation of diastolic pressure is due to marked decrease in the amplitude of the pulse wave associated with only slight reduction in the mean pressure.

2. In normal subjects, application of the right amount of pressure to the upper arm will often cause elevation of diastolic pressure in the brachial artery below the site of compression. In a typical experiment, two blood pressure cuffs were applied to the arm: one immediately above the elbow, the other just below the shoulder. The upper cuff was used to apply pressure, the lower for estimation of the blood pressure. With the upper cuff deflated, the blood pressure was 110/72, the "normal" blood pressure for this subject. With the upper cuff inflated to a pressure of 90 mm. Hg, which caused definite decrease in the volume of the pulse at the wrist, the blood pressure was 88/80.

3. In aortic stenosis of moderate or high grade, the diastolic pressure is often slightly or moderately elevated. This elevation is a result of decrease in the amplitude of the pulse wave due to slow systolic discharge of the left ventricle.

In some cases of coarctation, mean pressure in the femoral arteries is actually above normal, although in all cases, it is lower than mean pressure in the brachial arteries. This elevation does not necessarily signify the presence of arteriolar constriction in the lower extremities, but may just as well be due to hypoplasia and diminished capacity of the distal segment of the aorta and its branches. Such hypoplasia has been noted in many cases at necropsy.⁹

CONCLUSIONS

The evidence at hand does not afford proof for the existence of a general increase in arteriolar tone throughout the body in coarctation of the aorta. Hypertension in the arms and elevation of diastolic pressure in the legs both may be explained by the mechanical effects of the lesion. Consideration of the results of recent studies does not warrant abandonment of the concept presented in 1931 by Blumgart, Lawrence, and Ernestene.⁴

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OBSERVATIONS CONCERNING THE INFLUENCE OF CALCIUM UPON THE ACTIONS OF A DIGITALIS GLYCOSIDE

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THE possible relationship of calcium and digitalis compounds with respect to their combined effects upon the heart is still not completely known. Clark,¹ working with the frog's heart, was the first to observe that digitoxin did not affect its typical cardiac actions in the absence of calcium. Later, Ransom² found that strophanthin markedly improved the beating of a perfused frog's heart if the latter had been weakened previously by the removal of calcium from the perfusion fluid. Loewi³ confirmed these results, emphasizing the similarity of cardiac effects following either the administration of strophanthin or excess calcium. It is probable that the concept of synergism between calcium and digitalis compounds had its origin in the results of these experimenters.

Later workers approached the problem by studies of the intact mammalian heart following exposure either to digitalis or calcium. Gold and Edwards,⁴ working on dogs, concluded that a marked synergism existed between ouabain and calcium. Lieberman,⁵ Bower and Mengle,⁶ McGuigan and Higgins,⁷ and Smith and associates,^{8,9} however, could find little evidence of any synergism existing between calcium and digitalis compounds.

In the present communication, the results of studies concerning the actions of calcium and the digitalis glycoside, lanatoside C, upon the embryonic duck heart are reported. These results indicate that the calcium ion and the glycoside are not synergistic. More important, perhaps, the results also indicate that the physiologic activity of the glycoside employed is not impaired by the *total* absence of calcium.

METHODS

The manner in which the embryonic duck heart, devoid of nervous elements,^{10,11} can be employed for the study of the cardiac effects of a digitalis glycoside has already been described. In the presence of sufficient digitalis glycoside, the embryonic heart immediately increases its rate of beating, exhibiting a hypertonic type of contraction and beginning to have auriculoventricular block, then becomes irregular, slower, and finally ceases. The time of occurrence

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of A-V block and the duration of beating at any given temperature have been found¹⁰ to bear a close quantitative relationship to the concentration of glycoside. Thus, the amount of glycoside in contact with an embryonic heart can be estimated by the chronological sequence of the development of A-V block and cessation of beating.

Tyrodé's solution was employed as the basic medium, and changes in its calcium or potassium content were made either by removing or adding the chlorides of either cation. Lanatoside C (derived from *Digitalis lanata*) was used in all experiments and a fresh ampule of it was opened for each day's experiments.

RESULTS

The Effect of Variations in Calcium Ion Concentration Upon the Embryonic Duck Heart.—As Table I, A indicates, variations from 5.0 to 100 mg. of calcium chloride per 100 c.c. of Tyrodé's solution had little effect upon the cardiodynamics of the embryonic hearts, except for a slowing of rate and slight irregularity of rhythm of hearts immersed in Tyrodé's solution containing excess calcium (Table I, A, 5). Hearts beating in Tyrodé's solution containing no calcium (Table I, A, 2), however, beat weakly, and twelve of thirty-two hearts (37.5 per cent) exhibited A-V block after an average period of fifteen minutes. In summary, at no concentration of calcium studied were hearts observed to behave like those exposed to digitalis glycoside.

TABLE I. THE EFFECTS OF VARIATIONS IN THE CONCENTRATION OF CALCIUM ON NORMAL EMBRYONIC HEARTS AND ON THOSE EXPOSED TO DIGITALIS GLYCOSIDE

	CALCIUM CONC. (MG. %)	NUMBER OF HEARTS	SIZE OF HEARTS*	RATE (PER MIN.)	A-V BLOCK (NO. HEARTS)	ONSET OF A-V BLOCK (MIN.)	RHYTHM	FORCE OF BEAT	DURATION OF CON- TRACTIONS (MIN.)
<i>A. No Digitalis Glycoside Present</i>									
1.†	20	15	28	59	0	—	Reg.	Vig.	Over 60
2.	0	32	31	66	12	15	Reg.	Weak	Over 60
3.	5	12	29	74	0	—	Reg.	Mod.	Over 60
4.	10	8	29	74	0	—	Reg.	Mod.	Over 60
5.	100	12	29	39	0	—	Irreg.	Vig.	Over 60
<i>B. With Digitalis Glycoside (0.001 Mg. Per c.c.)</i>									
1.‡	20	18	31	90	18	11	Irreg.	Vig.	22
2.	0	41	28	84	12	19	Irreg.	Mod.	34
3.	5	16	22	70	10	18	Irreg.	Mod.	27
4.	10	12	24	66	12	19	Irreg.	Mod.	26
5.	100	12	29	75	12	10	Irreg.	Vig.	22

*Equals the diameter in millimeters of the vascular sinus surrounding the embryo.

†Equals a control solution or ordinary Tyrodé's solution.

‡Equals a control solution of ordinary Tyrodé's solution plus 0.001 mg. of digitalis glycoside per cubic centimeter.

The Effect of Variations in Calcium Concentration Upon the Activity of a Toxic Amount of Digitalis Glycoside.—The immersion of eighteen duck hearts in ordinary Tyrode's solution containing the normal amount of calcium chloride (20 mg. per cent) and 0.001 mg. of lanatoside C per cubic centimeter was found (Table I, B, 1) to result in A-V block in each of the hearts after an average period of eleven minutes (range, nine to thirteen minutes) and in permanent cessation of beating after an average period of twenty-two minutes (range, thirteen to thirty minutes). This toxic action of the glycoside was markedly but not completely inhibited, however, if all calcium was removed from Tyrode's solution. Thus, only twelve of forty-one hearts (29 per cent) exposed to glycoside in the absence of calcium exhibited A-V block and then only after nineteen minutes (Table I, B, 2). This same series also continued to beat for thirty-four minutes. Hearts exposed to the same amount of glycoside in Tyrode's solution containing 5.0 or 10 mg. per cent of calcium chloride (see Table I, B, 3 and 4) also showed somewhat lessened sensitivity to the glycoside as compared with the control hearts. Excess calcium, however, was not found to enhance the action of digitalis glycoside, as hearts immersed in Tyrode's solution containing 100 mg. per cent of calcium chloride did not exhibit A-V block or cease beating any faster than did the control hearts (Table I, B, 5). These results indicated that, whereas the withdrawal of calcium from Tyrode's solution partially inhibited the action of glycoside, an excess amount of calcium did not enhance the action of the cardiac drug.

The Effect of Excess Calcium Upon the Sensitivity of the Embryonic Duck Heart to Varying Amounts of Digitalis Glycoside.—Although the foregoing experiment appeared to indicate that calcium bore neither synergistic nor specific additive relationship to the action of a digitalis glycoside, it was conceivable that the extreme toxicity of the quantity of glycoside employed precluded further acceleration of its activity, despite the type of agent added.

It was found, however, that the addition of excess calcium (100 mg. per cent) did not enhance the action of digitalis glycoside at any concentration of the latter employed (Table II). Thus, hearts exposed to 0.001, 0.0005, and 0.0001 mg. of glycoside per cubic centimeter of *normal* Tyrode's solution exhibited A-V block and cessation of beating just as often and as rapidly as did hearts exposed to the same amounts of glycoside plus excess calcium (Compare Table II, A and B). Moreover, neither hearts in normal Tyrode's solution nor hearts in excess calcium reacted to 0.00001 mg. of glycoside per cubic centimeter. These results indicated that excess calcium did not render the duck heart more sensitive to the effects of digitalis glycoside at any concentration.

The Behavior of the Embryonic Duck Heart Exposed to Digitalis Glycoside in Tyrode's Solution Without Potassium and Tyrode's Solution Without Potassium or Calcium.—The preceding experimental observations, while indicating that no synergism existed between calcium and digitalis glycoside, nevertheless also suggested that the action of the glycoside was markedly interfered with if calcium was diminished or absent. Since the withdrawal of calcium from Tyrode's solution is known to accentuate the effect of the potassium still remain-

TABLE II. THE EFFECT OF EXCESS CALCIUM ON THE SENSITIVITY OF EMBRYONIC HEARTS TO VARIOUS QUANTITIES OF DIGITALIS GLYCOSIDE

	DIGITALIS GLYCOSIDE (MG/C.C.)	NUMBER OF HEARTS	SIZE OF HEARTS*	A-V BLOCK (NO. HEARTS)	ONSET OF A-V BLOCK (MIN.)	DURATION OF CONTRACTIONS (MIN.)
<i>A.. Hearts in Ordinary Tyrode's Solution</i>						
1.	0.001	18	31	18	11	22
2.	0.0005	15	33	15	14	42
3.	0.0001	12	31	12	18	46
4.	0.00005	18	32	14	39	Over 60
5.	0.00001	16	28	0	—	Over 60
<i>B. Hearts in Tyrode's Solution With High Calcium (100 Mg. %)</i>						
1.	0.001	12	29	12	10	22
2.	0.0005	14	22	14	12	38
3.	0.0001	13	32	12	18	41
4.	0.00005	20	28	6	45	Over 60
5.	0.00001	10	30	0	—	Over 60

*Equals the diameter in millimeters of the vascular sinus surrounding the embryo.

ing in this type of solution, it was thought possible that this last fact might well explain the diminished action of digitalis glycoside after the withdrawal of calcium. In other words, the known action of potassium in inhibiting the action of digitalis compounds^{12,15} would be accentuated following the removal of calcium. Control studies were made on hearts beating in the absence of potassium and also in the absence of both potassium and calcium (Table III, A, 2 and 3). Auriculo-ventricular block and cessation of beating occurred as frequently and as rapidly in both types of solution.

Eleven hearts immersed in Tyrode's solution containing no potassium but 0.001 mg. of glycoside per cubic centimeter exhibited A-V block after five minutes and ceased to beat after seventeen minutes. These results when compared with those obtained on hearts exposed to the same quantity of glycoside in normal Tyrode's solution (compare Table III, B, 1 and 2) indicated that the absence of potassium markedly accentuated the activity of digitalis glycoside. Furthermore, when twenty-three hearts were exposed to the same quantity of digitalis in Tyrode's solution containing neither calcium nor potassium, it was found (see Table III, B, 3) that these hearts exhibited A-V block and cessation of beating as rapidly as did those immersed in Tyrode's solution containing calcium but no potassium (compare Table III, B, 2 and 3). In summary, calcium was not found to be necessary for the action of digitalis glycoside if potassium was absent.

TABLE III. THE EFFECTS OF POTASSIUM AND CALCIUM DEPRIVATION ON NORMAL EMBRYONIC HEARTS AND THOSE EXPOSED TO DIGITALIS GLYCOSIDE

	TYPE OF SOLUTION	NUMBER OF HEARTS	SIZE OF HEARTS	RATE	A-V BLOCK (NO.)	ONSET OF A-V BLOCK (MIN.)	DURATION OF CONTRACTION (MIN.)
<i>A. No Digitalis Glycoside Present</i>							
1.	Normal Tyrode's	15	28	59	0	—	Over 60
2.	Tyrode's—No K	29	29	86	21	14	29
3.	Tyrode's—No K, No Ca	18	26	85	14	15	29
<i>B. With Digitalis Glycoside (0.001 Mg. Per c.c.)</i>							
1.	Normal Tyrode's	18	31	90	18	11	22
2.	Tyrode's—No K	11	28	105	11	5	17
3.	Tyrode's—No K, No Ca	23	26	104	23	6	15

DISCUSSION

There appeared to be little doubt from our results that the action of calcium upon the embryonic duck heart was radically different from that of the digitalis glycoside employed. Likewise, no variation in calcium was found to give results which might suggest that a synergism existed between it and digitalis glycoside in their effects upon the duck heart.

Despite the lack of evidence suggesting a synergism between excess calcium and glycoside, our studies did indicate that very low concentrations of calcium in Tyrode's solution retarded the action of digitalis glycoside. This latter phenomenon was found to be due not to the absence of the calcium ion, per se, but to the relative physiologic preponderance of the potassium ion which resulted after the withdrawal of calcium. Thus, it was this accentuation of the physiologic activity of potassium with its increased inhibition of digitalis glycoside^{12,13} which accounted for the diminished action of digitalis glycoside in the absence of calcium. This was shown clearly in those experiments in which hearts immersed in Tyrode's solution containing neither calcium nor potassium reacted as much to digitalis glycoside as did those immersed in Tyrode's solution lacking only potassium. It should be emphasized also that Clark¹ employed solutions containing potassium, and his withdrawal of calcium from these same solutions could have inhibited glycoside in the same indirect manner which has been discussed.

SUMMARY

The embryonic duck heart was employed for experiments in which the relationship of calcium and a digitalis glycoside was studied. It was found that the effects of this glycoside were not enhanced by excessive amounts of calcium.

Finally, it was discovered that the digitalis glycoside studied could exert its typical and usual affects in the complete absence of calcium.

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A NOMOGRAM FOR RATE CORRECTION OF THE Q-T INTERVAL IN THE ELECTROCARDIOGRAM

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TARAN and Szilagyi¹ have shown recently that prolongation of the Q-T interval is a valuable diagnostic sign of rheumatic carditis in children. It is probable that measurement of the Q-T interval will now become a routine procedure. Because it is necessary to standardize the Q-T for rate with one of several formulas which require the application of time and arithmetic, it occurred to us that a nomogram for making the rate correction would be useful.

There are several empirical formulas which may be used to standardize the Q-T interval for rate. These formulas were recently reviewed by Schlamowitz,² who added one of his own. The several formulas yield figures which are approximately the same. Bazett's formula³ is the simplest and has been used more widely than any other. We chose, therefore, to use the Bazett formula in our nomogram.

Bazett's formula is $Q-T = K\sqrt{R-R}$, where $Q-T$ = Q-T interval in seconds, $R-R$ = cycle length in seconds, and K = a constant. Bazett's constant K is 0.370 ± 0.024 in men and 0.400 ± 0.040 in women. In applying the formula, one compares the measured Q-T with the normal Q-T. The normal Q-T is found from the formula in which the heart cycle length and the Bazett constant are known. There are tables based on this formula which give the normal Q-T associated with a given R-R.⁵ One may then compare the normal Q-T with the measured Q-T.

The formula is used more generally in another way, namely: $\frac{Q-T}{\sqrt{R-R}} = K$.

The measured Q-T is divided by the square root of the measured R-R. The quotient obtained, K , is then compared with Bazett's K . This method has an advantage in that one need remember only the normal K (or K 's) rather than the many normal Q-T's corresponding to various heart rates. This method was used by Barker and associates,⁵ for example, in their study of the Q-T interval in hypocalcemia.

Taran and Szilagyi¹ also used this method and, in addition, introduced a new thought. He preferred to call the K the Q-T corrected for rate, or the Q-Tc.

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We feel that this concept of $Q-T_c$ represents an advantage. Bazett's formula may thus be considered to standardize the $Q-T$ interval to a heart rate of 60 per minute or to a cycle length (R-R) of one second.

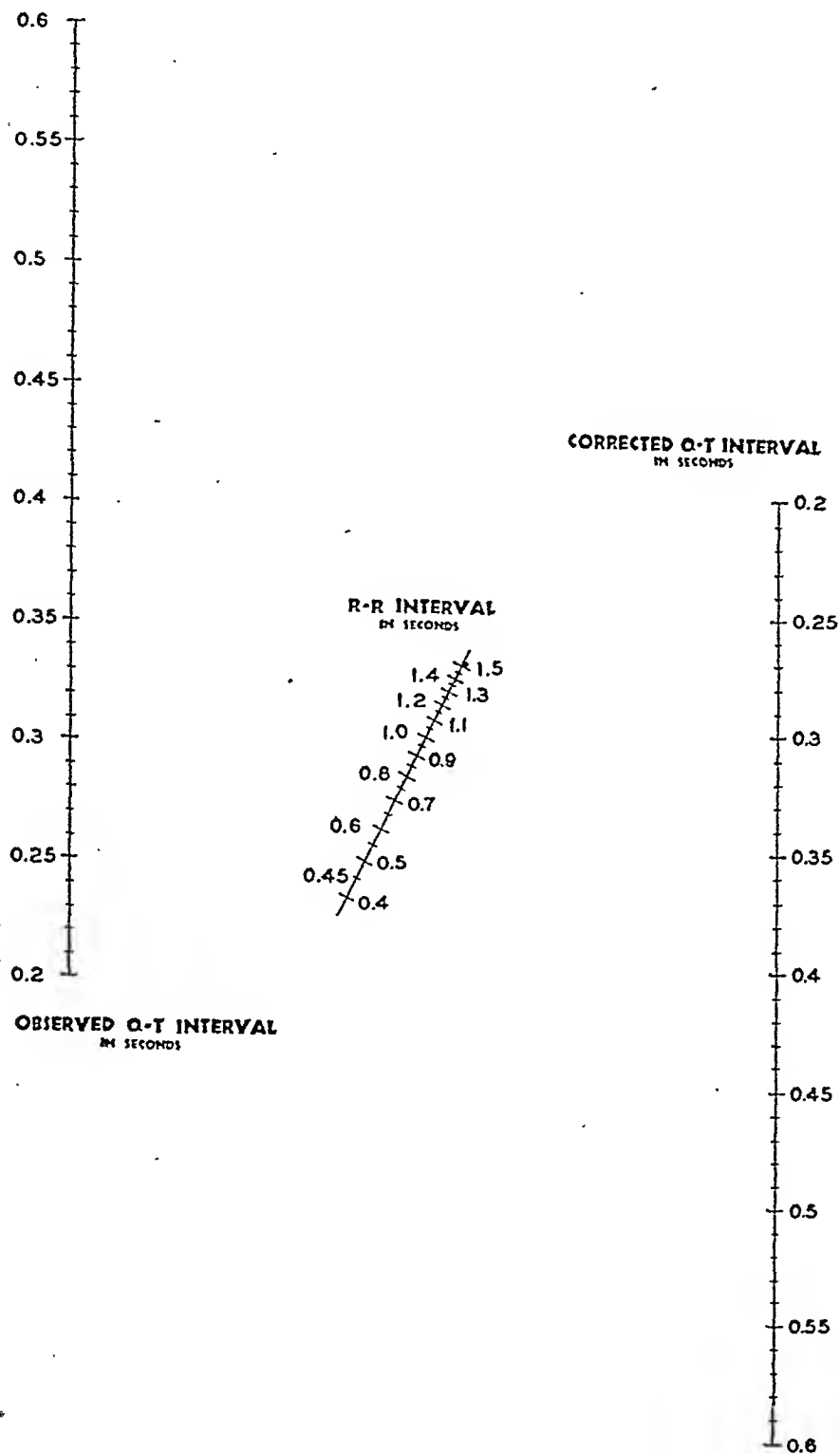


Fig. 1.—Nomogram for rate correction of $Q-T$ interval. See text for method of use.

According to Ashman and Hull,⁶ who have made thousands of measurements of the $Q-T$ interval, the normal $Q-T$ for an R-R of 1.0 second is: men and children, 0.386; women, 0.396. The upper limits of normal are: men and children, 0.422; women, 0.432.

The nomogram, Fig. 1, is used as follows: From the actual Q-T (left column) and R-R (central column), one may draw a line to the right column and read off the Q-Tc. This figure may then be compared with the normal Q-Tc. We have used as our straight edge a piece of vinylite or x-ray film with a scratch several inches long which has been inked in.

Instead of a nomogram, a slide rule may be used. The ordinary slide rule lends itself readily to the Bazett formula. A special slide rule could easily be devised.

The method of measurement of the Q-T interval deserves mention. The beginning of the QRS or the end of the T wave may be isoelectric in any single lead. Therefore, that lead in which the Q-T interval is longest is the proper lead in which to make the measurements. In that lead, several Q-T and R-R intervals should be measured and the resulting Q-Tc's averaged. It is incorrect to measure several Q-T intervals, then several R-R intervals, and divide the average Q-T by the square root of the averaged R-R.

SUMMARY

1. A nomogram for correcting the Q-T interval for heart rate, according to Bazett's formula, is presented.
2. The Q-T corrected for rate represents the Q-T corresponding to a heart rate of 60 (cycle length 1.0 second). It is suggested that it be known as the Q-Tc.
3. The lead in which the Q-T interval is largest is the correct lead in which to measure it.

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Clinical Reports

HEMOCHROMATOSIS WITH DEATH FROM HEART FAILURE

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UNTIL recent years, little attention was paid to cardiac symptoms as a manifestation of hemochromatosis. In Sheldon's¹ classic monograph on this disease, myocardial failure is mentioned only as an incidental cause of death. Althausen and Kerr² stressed the cardiac findings in three patients and suggested that, with the prolongation of life possible with insulin control of diabetes, cardiac symptoms would be found more frequently. We are in agreement with this prediction.

Blumer and Nesbit³ and Petit⁴ have reported patients with hemochromatosis with cardiac failure, and all three authors have extensively discussed this complication. Murray Lyon⁵ reported three cases of patients with hemochromatosis, two of whom died of heart failure. Bloom⁶ and John⁷ have described patients with hemochromatosis who showed unmistakable evidence of cardiac disorder. A large group of French authors⁸⁻¹⁵ have stressed the cardiac features of hemochromatosis and give to this symptom complex the name "syndrome endocrino-hepato-cardiaque." The most comprehensive discussions are those of de Gennes and co-workers¹¹ and of Oumansky and Longuet.¹⁴

To call attention again to the importance of myocardial changes in this disease, the following case is presented.

CASE REPORT

L. R., a 31-year-old farmer, was admitted to the Veterans Administration Hospital, Richmond, Va., on April 25, 1946, by transfer from the Medical College of Virginia Hospital. He had been admitted there on April 21 in diabetic coma, which had been successfully treated, and diabetes was fairly well controlled at the time of transfer.

The patient had regarded himself as being in good health all his life and had served in the Army from Sept. 9, 1943, until Feb. 1, 1946. During this period, he had been stationed in the Philippines and in New Guinea and had served as a cook and as a welder. He had had four Army

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hospitalizations, three for impetigo and one for stomach trouble. He knew of no urinary findings on these admissions. In November, 1945, he began to lose weight. He returned to the United States on points and received an honorable discharge Feb. 1, 1946. He stated that no urinalysis was done at this time. During the next three months he noticed nocturia, polyuria, polydipsia, increasing weakness, and weight loss of 25 pounds. On April 19 he began to be drowsy, grew nauseated and vomited, and lapsed into unconsciousness. Diabetic coma was diagnosed by his family physician and he was referred to the hospital for treatment.

On admission to the Medical College of Virginia Hospital, the patient was semicomatose, dehydrated, and exhibited Kussmaul breathing. The skin was of a dusky, brownish color, and the liver edge was palpable at the level of the umbilicus. Urine showed 4 plus sugar and 4 plus acetone. Blood sugar was 800 mg. per cent. The carbon dioxide combining power was 20 volumes per cent. During the next twelve hours, the patient received 970 units of insulin, 4000 c.c. of normal saline, and 1,000 c.c. of 5 per cent glucose in saline, with good clinical and chemical recovery from coma. The patient was placed on a suitable diet and maintained on 30 units of insulin before each meal. Hemochromatosis was suspected because of the dusky skin pigmentation and hepatic enlargement. The urine sediment was examined for hemosiderin and was reported negative. On April 25, the patient was transferred to the Veterans Administration Hospital.

On admission to this hospital, the patient was alert and in no discomfort. He was thin and emaciated, and the skin was of a dusky tan color with a suggestion of a leaden hue when the light fell across it. Blood pressure was 95/55. The liver was greatly enlarged, the firm edge being palpable at the level of the umbilicus and extending across into the left upper quadrant. The spleen was not palpable. The heart was apparently of normal size, with regular rhythm. The sounds were distant, but no murmurs were heard. The lungs were clear. Deep reflexes were hypoactive in the lower extremities. Examination otherwise was entirely negative.

The history was reviewed and was essentially as has been given. The patient stated that during his last months in the Army, friends commented on the darkening of his skin. He knew of no diabetes in his family. He had never been jaundiced.

The urine contained 4 plus sugar but no acetone, and the fasting blood sugar the day after admission was 307 mg. per cent. Hemoglobin was 100 per cent; white blood cells, 6,100 with a normal differential count. Bromsulfalein test done on May 2, using a dose of 5 mg. per kilogram of body weight, showed no retention of dye in forty-five minutes.

The patient was placed on the same diet he had been receiving, and dosage of 30 units of regular insulin before each meal was continued. Then, because of suspected liver disease, supplementary feedings of skimmed milk and choline, 6.0 Gm. daily, were added. Diabetes remained well controlled. On May 2, the patient was changed to protamine zinc insulin and was soon regulated on 15 units of regular insulin and 50 units of protamine. He was allowed up and urged to be active. His diet was gradually increased, and his insulin was increased to 20 units of regular and 60 units of protamine. With the patient's increased activity his diabetes became more difficult to control; on the same insulin dosage his blood sugar showed erratic changes, and some hypoglycemic levels were found, although no frank reactions occurred. During this period, the patient appeared to be quite well and gained in weight from 111 to 123 pounds. There was no change in the size of the liver. The blood pressure, which had been low on hospital admission, had risen to 110/70 and was maintained at this level.

On the night of May 29, the patient complained of a peculiar precordial fluttering sensation with some shortness of breath. Examination showed a tachycardia of 160 per minute with some irregularity which did not respond to carotid sinus pressure. With sedation the rate slowed and the next morning was 100, with occasional extrasystoles. Blood sugar on this morning was found to be down to 50 mg. per cent. He was given extra feedings of orange juice, and his insulin dosage was reduced. No subsequent hypoglycemia occurred. The patient, however, continued to complain of precordial fluttering and increasing shortness of breath. Electrocardiogram on May 31 showed occasional ventricular premature contractions, low voltage of the QRS complex in all leads, deep S₂ and S₃, diphasic T₁ and T₂, and inverted T₄ (Fig. 1). These changes indicated myocardial disease and an old anterior infarction was suggested.

The patient became progressively more dyspneic. By June 1 it was apparent that the liver had become larger, and extended 5 cm. below the umbilicus. Distention of the neck veins was visible even with the patient upright. The heart appeared to be enlarging. The rate remained around 100 with more frequent extrasystoles. No murmurs or rubs were heard. The blood pressure fell to 90/55. The lungs remained clear. Quinidine, 3 grains every four hours, was begun. The rhythm became more regular, but dyspnea, orthopnea, and evidence of right heart failure became more pronounced. On June 3, the neck veins were grossly distended, and with the patient recumbent, one vein in the left side of the neck became enlarged to the size of an egg. The heart appeared enlarged to both left and right. The sounds were audible, but weak. The second pulmonic sound was accentuated, but no other abnormal sounds were heard. Blood pressure varied between 90/70 and 80/60.

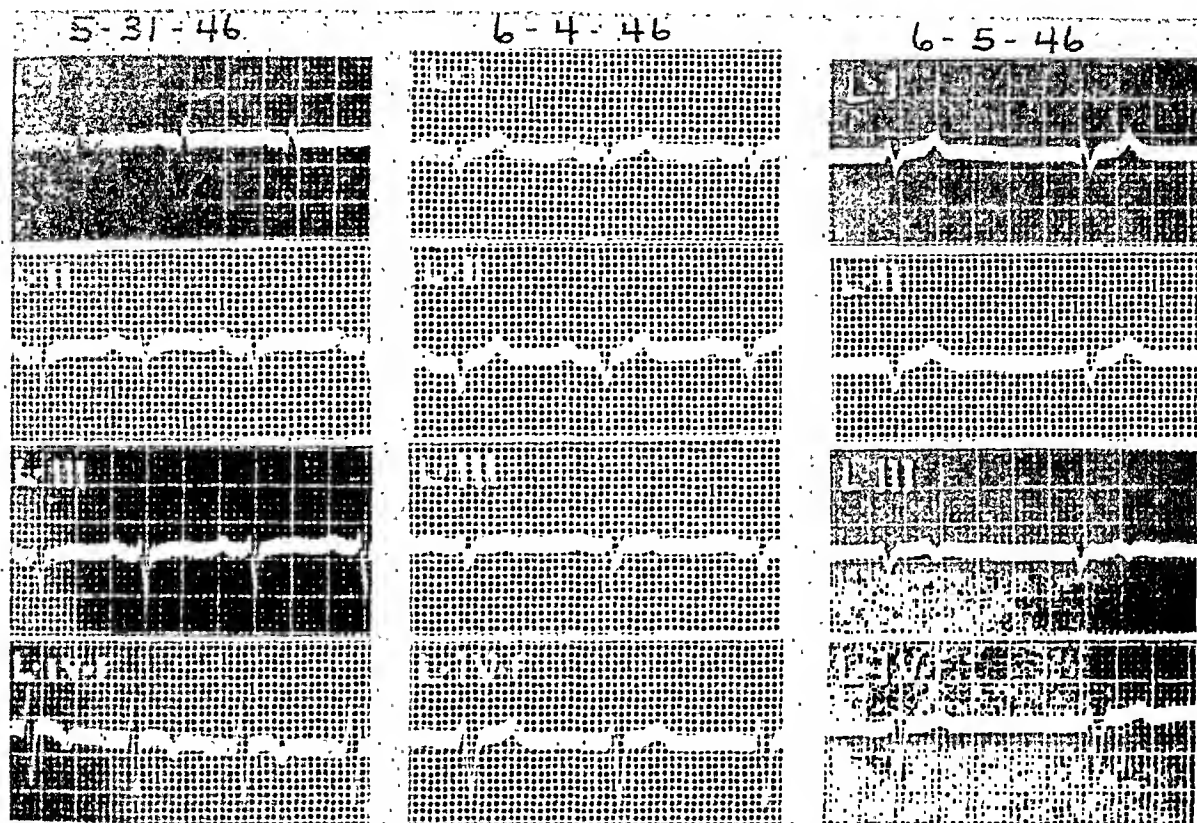


Fig. 1.—Serial electrocardiograms. On May 31, 1946, ventricular premature contractions were present but do not show on the segments reproduced here. Note the development of complete sino-auricular block in the tracing of June 5, 1946.

Pericardial effusion was suspected. Fluoroscopy and films were taken (Fig. 2). The heart was enlarged in all dimensions. Cardiac pulsations were visible, but of small amplitude. Films in the supine position revealed a peculiar widening of the mediastinal shadow which was difficult to interpret. Atelectasis of the right lower lobe with elevation of the right diaphragm was also demonstrated.

Pericardiocentesis was attempted through the xyphoid approach, but no fluid was obtained. Various diagnoses were considered, including acute cor pulmonale, myocardial infarction, right auricular thrombus formation, and others. The consensus, however, was that the patient was suffering from some type of diffuse myocardial disease with failure predominantly of the right-sided type. Hemochromatosis involving the myocardium was considered to be a likely factor, but some other acute process was thought to be present as well. Digitalis was withheld because it was considered to be of little value in this type of failure and potentially dangerous in an already irritable heart. The patient was kept propped upright in an oxygen tent, Karell feedings were given,

and Mercupurin was given for diuresis. Quinidine was continued. Regular insulin was given in sufficient amounts to prevent ketosis, but the diabetes was not strictly controlled. Large doses of thiamin were given empirically.

The patient showed no response to these measures, and his condition became steadily worse. The neck veins remained distended, the liver enlarged, and sacral and ankle edema developed. The lungs remained clear throughout. The patient remained afebrile and conscious until terminally. The pulse rate remained peculiarly slow, not exceeding 100 per minute, and was fairly regular until the end. However, cardiac action appeared to become weaker. Subsequent electrocardiograms showed low voltage and slurring of QRS complexes, return of upright T waves, and the development of sinoauricular block (Fig. 1). The peripheral pulse became more feeble, blood pressure dropped, and cyanosis developed. The patient died on June 5.

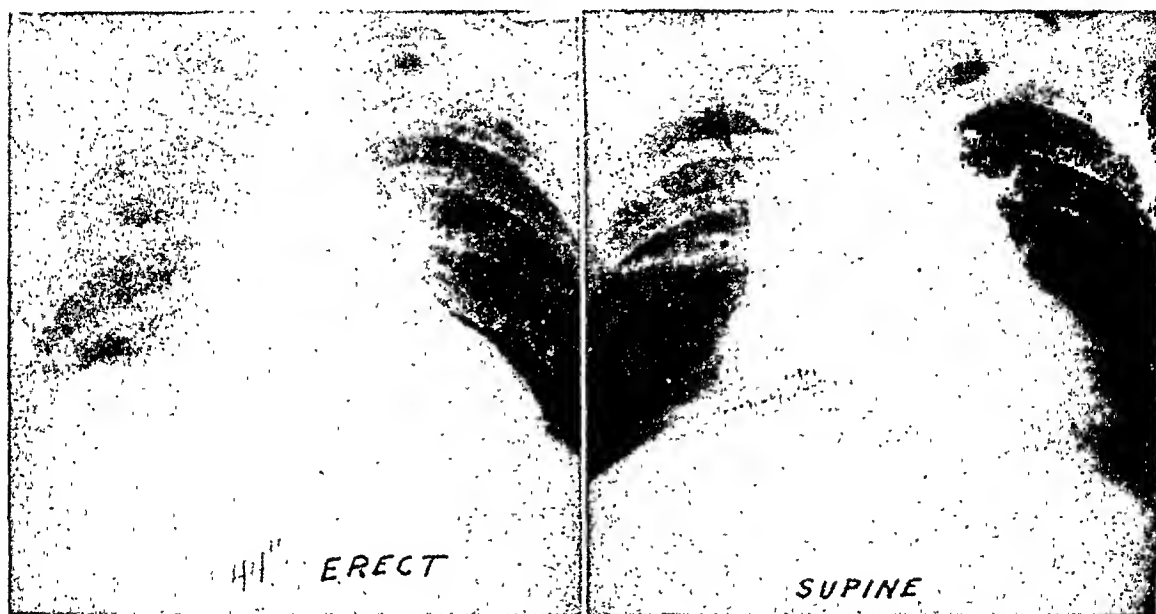


Fig. 2.—Erect and supine chest films taken at 44-inch target distance. See text for discussion.

*Autopsy Findings.**—The skin had a markedly yellow color, with a large number of frecklelike pigment spots over the entire body. The pleural cavities contained 700 c.c. of turbid yellow fluid in the right side and 400 c.c. in the left. The peritoneal cavity contained 1,000 c.c. of similar fluid. The lungs showed atelectasis of the right lower lobe and of the posterior portion of the left lower lobe. No obstruction of the bronchi or of the pulmonary vessels could be found.

The heart was dilated to a remarkable extent, filling approximately one-half of the anterior chest area. All chambers were dilated, particularly the right atrium which formed a large bulge on the right margin. The heart muscle was of a peculiar coppery brown color, and was thin and flabby. Small ante-mortem thrombi were present in the tip of the right auricular appendage and in the tip of the left ventricle, adherent to the endocardium. There was no evidence of infarction of the myocardium. The coronary vessels were patent. The heart valves were normal. The pericardial cavity contained only 15 c.c. of yellow fluid. The aorta, pulmonary vessels, and venae cavae were dissected out and showed no thrombosis. There was remarkable dilatation of the superior vena cava and of the jugular veins.

The spleen weighed 275 grams. It was soft and dark red with a congested firm pulp on section. The liver was very large, weighing 3,300 grams. It was coppery brown in color and its surface showed a coarse, granular appearance. On section, the dark brown color extended throughout, the

*Autopsy was done by Dr. George Z. Williams two hours after death.

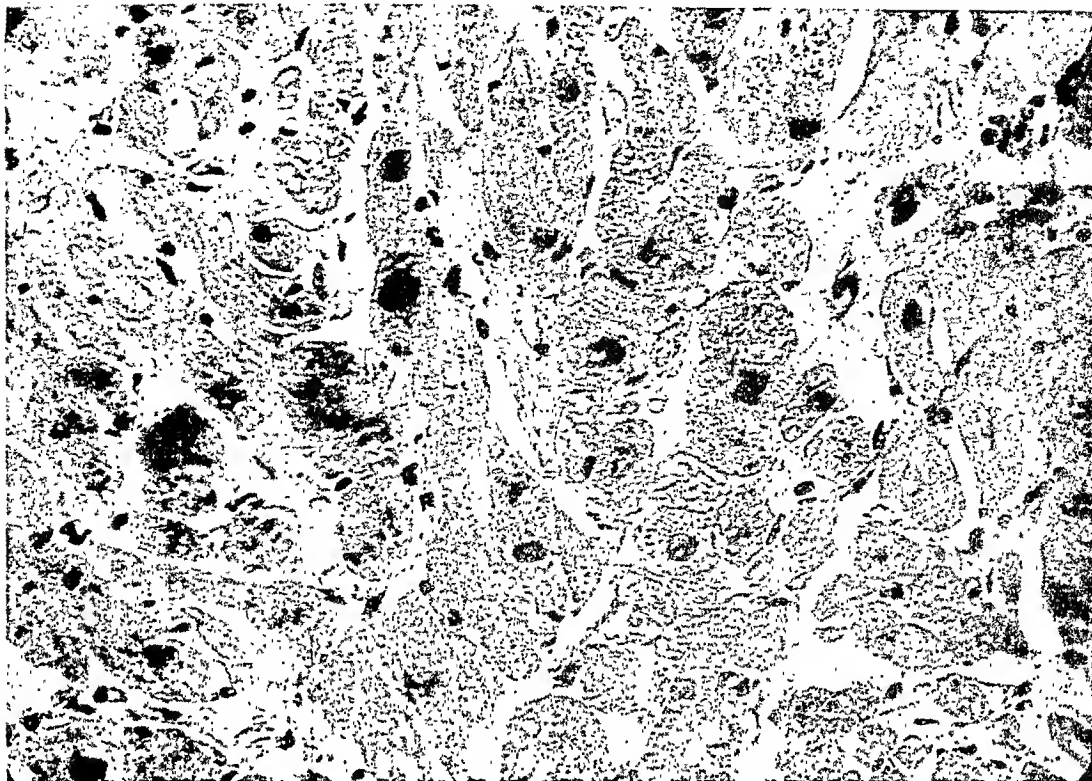


Fig. 3.—Myocardium, showing swelling and vacuolar degeneration of muscle, characteristic of the entire heart. (Hematoxylin and eosin stain, $\times 360$.)



Fig. 4.—Myocardium, showing iron granule deposits in muscle fibers. (Iron stain, $\times 180$.)

consistency was firm, and interlobar markings were accentuated. The gall bladder and ducts appeared normal. The pancreas was small, weighing 100 grams, and was of a chocolate brown color. Lymph nodes in the region of the liver and pancreas were also chocolate brown in color. The kidneys, adrenal glands, and gastrointestinal tract appeared normal on gross examination and section.

Microscopic Examination.—Sections of the heart (Figs. 3 and 4) showed marked swelling of the muscle cells and considerable irregularity in the amount of connective tissue between the muscle bundles. Individual cells were lost and replaced by connective tissue, but no dense fibrosis was seen. The nuclei of the surviving cells varied considerably in size. The cytoplasm of the muscle cells was light-staining and markedly granular with much space between the fibril granules. Many of the muscle cells contained much greenish brown, fine dustlike pigment. Iron stains showed this pigment to give a positive Prussian blue reaction. In the connective tissue between the muscle cells and bundles, there were numerous endothelial-type cells and other phagocytes which also contained clumps of brown pigment yielding a positive reaction to iron stains. The vessels of the heart were not remarkable.

Sections from the atelectatic areas of the lungs showed complete alveolar collapse. Sections from other areas showed congestion and some heart failure cells, which gave the iron-positive staining reaction. Aside from these cells, no pigment deposition was seen.

Marked congestion of sinusoids and pulp of the spleen was present. Prussian blue staining revealed large amounts of iron pigment in both the endothelial cells and the connective tissue. In the lymph nodes there was marked pigmentation of the reticulo-endothelial cells and also of the elastic tissue of the media of adjacent blood vessels, giving a positive iron stain.

In the liver there was moderate increase of the connective tissue in the portal areas with distortion of the lobules caused by regenerating liver cells. The liver cells were diffusely infiltrated with large amounts of greenish brown pigment which gave a positive iron stain. Many of these cells showed swelling and other degenerative changes. Pigment was conspicuously scanty in the areas of regenerating liver cells. Pigment deposits were heavy in the Kupffer cells of the sinusoids.

In the pancreas there was considerable fibrosis in the septa encroaching on the lobules. The islands of Langerhans were conspicuously decreased in number and those remaining were either atrophic or moderately hypertrophic. Iron pigment deposits were heavy in the connective tissue and within the islet cells in fine granular form.

There were marked iron pigment deposits in the cortical cells and less marked fine, dusty deposits in the medullary cells of the adrenals. No degenerative changes of the adrenal cells were seen. In the kidneys the glomeruli were normal. Small amounts of iron pigment were seen in the epithelial cells of the Henle loop tubules.

In sections of the skin small amounts of iron pigment were seen in the basal layer of the dermis and in the subcutaneous glandular structures.

The final pathologic diagnoses were: (1) hemochromatosis with marked iron deposition and pigmentation in heart, liver, lymph nodes, adrenal, and pancreas; (2) acute cardiac dilatation due to muscle atrophy and edema; (3) pulmonary atelectasis; and (4) marked visceral congestion.

DISCUSSION

Hemochromatosis became clinically evident in this patient at an unusually early age. In Sheldon's¹ series of cases, only 8 per cent of the patients were younger than 35 years. In most of these, hemochromatosis was discovered only at post mortem, the patients having died of some other cause. It is of interest that the French authors^{11,14} who describe the "syndrome endocrino-hepato-cardiaque" believe that it occurs at an age definitely below the average for most patients with hemochromatosis.

The diabetes of this patient was rapidly progressive, and he exhibited a narrow margin of balance between excessive glycosuria and hypoglycemic reactions. This is considered characteristic of the diabetes of hemochromatosis.^{16,17} The instability of the blood sugar is generally attributed to the co-existing liver cirrhosis with impairment of the ability of the liver to store glycogen.

The type of heart failure that this patient showed is of interest. Failure was acute in onset, rapidly progressive, and predominantly right sided. The widened mediastinal shadow was apparently due to enormous dilatation of the vena cava and its tributaries. At autopsy, all chambers of the heart were dilated, but particularly those on the right. The myocardial pigmentation and degeneration involved all the heart muscle diffusely. We believe that this patient had total heart failure, with the clinical effects chiefly apparent on the right side because of the relative anatomic weakness of the right ventricle as compared to the left. This type of total heart failure is seen in beriberi¹⁸ and in severe cases of acute rheumatic myocarditis.¹⁹ In the other cases of hemochromatosis with heart failure which we have reviewed, the failure has been more often right sided, but in many, both right- and left-sided failure have occurred.

Hypoglycemia was undoubtedly a factor in initiating heart failure in our patient. However, failure was severe and progressive after the blood sugar had returned to normal. We do not believe that a temporary episode of hypoglycemia, not severe enough to produce clinical shock, could produce irreversible changes in normal heart muscle. In heart muscle already damaged nearly to the limit of functional capacity, hypoglycemia might well tip the scales to the point of failure.

Digitalis was not used in our patient. It seemed of questionable value in such acute and generalized failure, and potentially dangerous in an already irritable heart. In some of the reported cases of heart failure in hemochromatosis, digitalis has been temporarily effective,^{2,12,13} but in the majority of these patients, it has proved of no value.^{1,11,14,15}

Petit⁴ has called attention to the frequency of cardiac arrhythmias when the heart is involved in hemochromatosis. In the twenty-one cases that we have reviewed, complete heart block is described four times,^{2,4,11} paroxysmal auricular tachycardia twice,^{5,6} and auricular fibrillation once. Many of the other patients exhibited frequent extrasystoles.

The French authors^{11,14} do not believe that heart failure in hemochromatosis can be attributed to damage to the heart muscle caused by pigment. They call attention to the frequency with which extensive pigment deposition in the heart is seen without heart failure. They have advanced the hypothesis that heart failure is caused by some unknown type of endocrine disturbance¹¹ or, more specifically, by adrenocortical deficiency.¹⁴ However, in all the cases reported in the English literature, extensive myocardial damage has been described, presumably resulting from pigment deposition. Althausen and Kerr² found diffuse myocardial sclerosis; Blumer and Nesbit,³ extensive fibrosis; Petit,⁴ areas of muscle atrophy and fibrosis; Bloom,⁶ vacuolization and fibrillar lysis; and John,⁷ extensive fatty degeneration. Our patient showed extensive degenerative

changes as well as pigment deposition in the heart muscle. We believe that these changes are sufficient to explain the cardiac failure. The adrenal glands contained pigment but showed no degenerative changes, and clinically, there was little to suggest adrenocortical insufficiency. The findings in our patient do not support the French point of view. We would agree with Blumer and Nesbit³, that when pigment deposits in the myocardium become severe enough to produce cellular degeneration, function is interfered with and heart failure can result.

CONCLUSIONS

1. A case of hemochromatosis with death from heart failure is reported.
2. The importance of myocardial damage in hemochromatosis is stressed.
3. The clinical features of the heart failure and the mechanism of its production are discussed.

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PAROXYSMAL TACHYCARDIA IN THE NEWBORN

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ALTHOUGH tachycardia with very rapid ventricular rates is not common in infants and children, when it does occur it may menace the life of the infant and, therefore, demands prompt and sometimes vigorous treatment. Hubbard¹ reviewed nineteen cases of paroxysmal tachycardia in infants under one-year of age and has reported nine cases in infants under eight months of age. Among sixteen patients treated with digitalis, there were fifteen who recovered and one who died as a result of proven sarcoma of the conduction system. Howard² reported a case of paroxysmal tachycardia in a 4-day-old infant who was treated with digitalis and recovered. Tarnower and Lattin³ described two cases of tachycardia, in one of which auricular flutter was present and in the other, atrioventricular tachycardia of nodal origin. The first case is of interest in that the rate varied from 140 to 225 per minute and was recognized before birth. The tachycardia persisted after birth and electrocardiographic studies revealed auricular flutter with varying degrees of block. Taran and Jennings⁴ have described a case of paroxysmal atrioventricular nodal tachycardia in a newborn infant, and emphasize the rarity of this disturbance by pointing out that it occurred only four times in sixteen years at the Massachusetts General Hospital.

We present the following case of a supraventricular tachycardia in a newborn infant, which produced alarming heart failure and was associated with a *Streptococcus viridans* infection in blood and urine.

CASE REPORT

R. W., a boy, was born at the Rockaway Beach Hospital July 3, 1946. The mother's pregnancy and labor were uneventful and the baby's condition at birth was normal. Both parents and three siblings were alive and well. There were no significant familial diseases. The patient's weight at birth was 8 pounds, 14 ounces. He was treated in accordance with the usual nursery routine. On the third day, the baby's temperature was 101° Fahrenheit. Examination at this time was negative. The possibility of dehydration fever prompted a hypodermoclysis. Twelve hours later, the infant became apathetic, the cry was feeble, and the respirations were shallow and rapid. For the first time cyanosis was present. Examination revealed a rapid heart rate, estimated to be over 200 beats per minute (Fig. 1). The rhythm was regular. Pressure over the carotid sinus brought an immediate response. The rate slowed to 130 beats per minute. With the slowing of the rate, the cyanosis disappeared and the respirations returned to normal. Ten

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minutes later, the tachycardia recurred but carotid sinus pressure at this time failed to influence the rate. The cyanosis reappeared, basal râles appeared in both lungs, and the liver edge became palpable below the costal margin. Mecholy1, 0.1 mg., was given subcutaneously and had no effect on the rate. Digitalis was then given parenterally in the following schedule, one-half cat unit

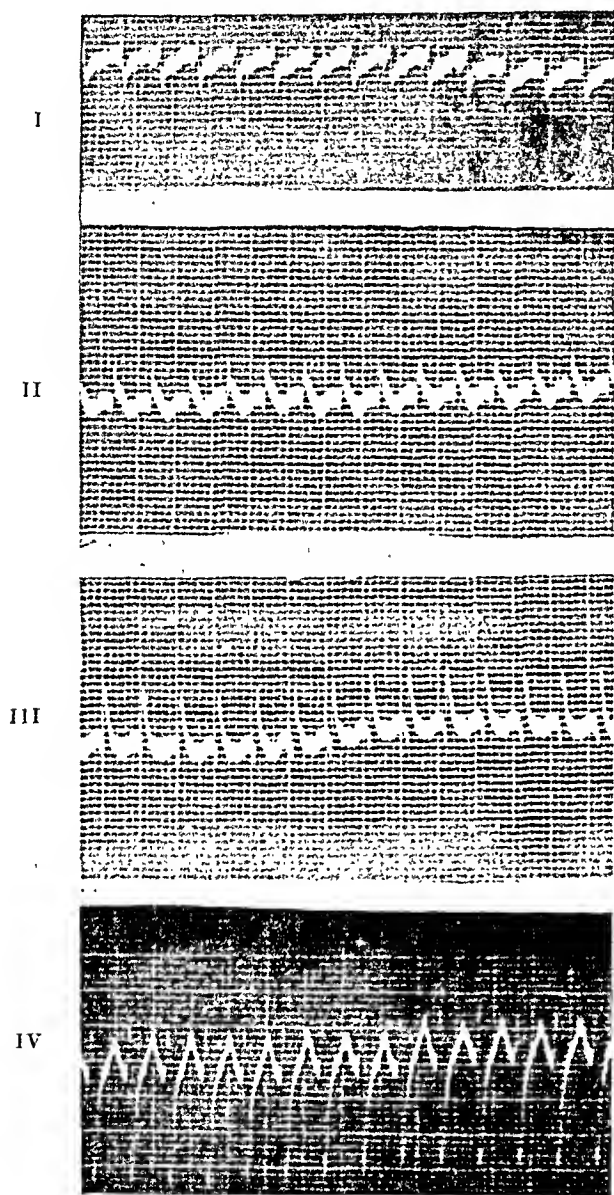


Fig. 1.

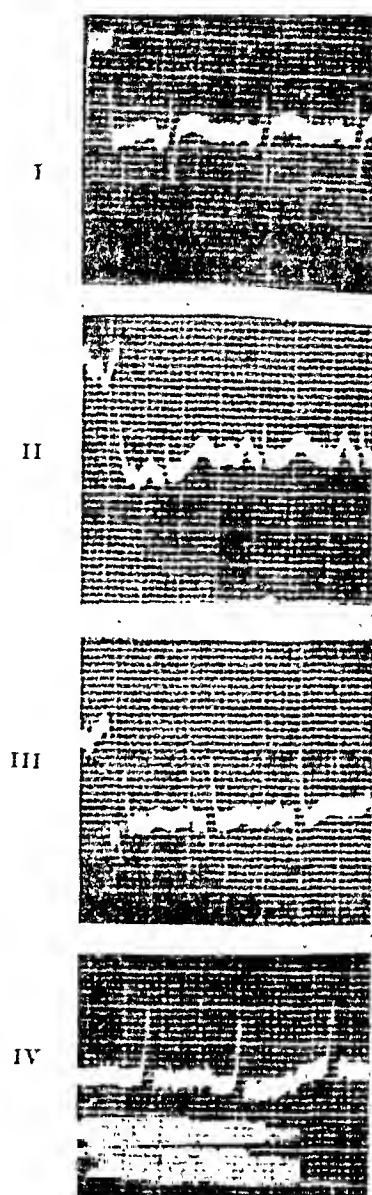


Fig. 2.

Fig. 1.—Electrocardiograph taken three days after birth. Auricular and ventricular rates 280 per minute. Sign. of congestive failure present.

Fig. 2.—Electrocardiogram taken thirteen days after birth. Auricular and ventricular rates 130 per minute. Normal sinus rhythm. No evidence of congestive failure.

was given immediately. Four hours later, one-fourth of a cat unit was given. The latter dose was repeated four hours later. One-quarter cat unit was then given twice a day for four days. After one cat unit had been administered, the rate of the heart returned to normal and the signs of congestive failure disappeared (Fig. 2). At the end of four days the digitalis was stopped and the heart rate remained normal.

The temperature could not be explained on the basis of the physical examination of the patient. A catheterized specimen of urine revealed numerous clumped pus cells. A pure culture of *Streptococcus viridans* was grown from the urine. A blood culture also showed the presence of *Streptococcus viridans*.

The patient was given 10,000 units of penicillin intramuscularly every three hours. Sulfadiazine, 2 Gm. per pound of body weight per day was also given. The temperature returned to normal in twenty-four hours but the blood cultures remained positive for one week. The urine was free of pus but urine culture still showed the presence of *Streptococcus viridans*. At the end of one week, the penicillin was discontinued. Sulfadiazine was continued for four weeks, at the end of which time the urine cultures became negative. At this period the cardiac status was normal and the child appeared clinically well. The weight at this time was ten pounds.

Blood chemistry showed the following values: nonprotein nitrogen, 40 mg.; sugar, 70 mg.; chlorides, 680 mg.; and cholesterol, 165 mg. per 100 c.c. of blood. Intravenous pyclography was negative. X-ray study of the chest showed a slightly enlarged cardiac shadow. The lungs were clear. There was no evidence of an enlarged thymus. A blood count, made on July 6, 1946, showed 14 Gm. of hemoglobin, 5,320,000 red blood cells, and 20,000 white blood cells. The differential count showed 47 per cent segmented and 10 per cent nonsegmented neutrophils, 6 per cent eosinophiles, and 37 per cent lymphocytes. On July 25, 1946, the blood count showed 9 Gm. of hemoglobin, 21,450 white blood cells, and 3,180,000 red blood cells. The differential count showed 76 per cent segmented and 12 per cent nonsegmented polymorphonuclear neutrophils, 1 per cent eosinophiles, and 11 per cent lymphocytes. A urinalysis done on July 11, 1946, was unimportant except for the presence of three to four red blood cells per high-power field and four to six white blood cells. Blood cultures made on July 9 and July 15, respectively, were positive for alpha *Streptococcus viridans*. A blood culture made on July 17 was negative. Urine cultures taken on July 15 and July 20 were positive for alpha *Streptococcus viridans*. On August 13, the urine culture was negative.

DISCUSSION

The nature of the tachycardia in this case cannot be positively identified. Auricular flutter with a 1:1 A-V ratio seems to be the most probable diagnosis. However, this condition cannot be positively established, nor can auricular or nodal paroxysmal tachycardia be eliminated. The only conclusions that can be drawn are that the tachycardia was not ventricular in origin and that it was dependent upon an ectopic rhythm; the latter seems to be well established by the prompt response to digitalis.

In spite of the uncertainty of the nature of the tachycardia, two facts stand out clearly: (1) the rapid ventricular rate produced a serious degree of heart failure and constituted a serious threat to life; and (2) the disturbance yielded promptly to digitalis. The use of digitalis in infants is not without danger.⁵⁻⁸ We, therefore, used the drug in this case in what seemed to us to be a cautious and safe manner.

A connection between the streptococcus infection and the tachycardia is difficult to establish. For this reason, the infection which yielded promptly to appropriate treatment has been presented as an incidental finding. The only fact that suggests a more direct causative relationship of the infection to the tachycardia is the fact that there was no return of the tachycardia after the elimination of the infection.

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Abstracts and Reviews

Selected Abstracts

Baker, E. C.: Clinical and Roentgenologic Evaluation of Venography. *Am. J. Roentgenol.* 58:603 (Nov.), 1947.

One thousand twenty-seven venograms were done with Diodrast as a contrast medium without any severe reaction. Twenty cubic centimeters of opaque material were injected during three minutes or more through a 25 or 26 gauge needle. Venipuncture was made through the skin in any vein below the ankle. A tourniquet was used only to aid in visualizing the vein and was removed before the injection was made. Three sets of stereoscopic exposures were made. One set covered an area from the ankle to the knee; a second set, the area of the upper leg, knee, and lower thigh; and the third set, the area of the upper thigh and lower pelvic area. The first exposure was made after the injection of approximately 8 c.c. (forty to sixty seconds after the start of the injection). The other exposures in succession were completed approximately at the time the injection was completed. With each exposure the quantity injected and elapsed time from the start of the injection were recorded.

Normal Subjects.—The greater portion of the contrast material enters the deep circulation fairly close to the ankle. A smaller quantity spreads through the superficial veins demonstrating external veins to the knee; usually the greater saphenous is well visualized. Young persons have straight veins and the Diodrast passes more rapidly upward than in older people who have slightly tortuous or dilated veins. In numerous normal subjects who remain motionless in the recumbent position the Diodrast may remain in the deep veins for five to twenty minutes after the injection. Any muscular activity forces the contrast material immediately upward.

Pathologic Findings.—In acute superficial block, the deep circulation is visualized up to the femoral fossa. The opaque material is seen in the superficial plexus to the site of the block. In another type of acute superficial block short lengths of straight, nondilated veins extend upward and apparently fade out. Two to four venograms showing the fading-out effect at same point should be done to confirm this finding.

In chronic superficial block, the veins are dilated and tortuous and the passage of the opaque material is usually slow. Small connecting veins extend inward toward or outward from the deep circulation for 1.0 to 3.0 cm. and appear to end abruptly in the tissues. Certain areas of superficial circulation are not demonstrable.

In acute partial or complete block of the deep circulation, definite evidence of acute superficial block is always demonstrable. The deep circulation of the involved area cannot be visualized.

In chronic block of the deep veins the deep vessels are partially or completely absent. The opaque material enters branches of the internal saphenous vein promptly, and by the time the region of the knee is reached all the contrast medium is returning upward through that vein. The entire saphenous vein is dilated and tortuous to the femoral fossa. Short lengths of communicating veins emerge from the internal saphenous vein and fade out into the tissues.

Complete block of the entire deep circulation of the leg and thigh frequently shows large dilated superficial varicosities.

Thrombi produce three types of shadows: In incomplete block, the head of the opaque column is usually concave; when the vein is incompletely obliterated a ragged, irregular area extending for a varying length is seen; finally, the opaque material may outline the walls and show a mass within the lumen.

Satisfactory venographic information can be obtained in probably 60 to 90 per cent of cases. Discontinuation of the study too soon in pathologic cases or improper timing of the exposures may possibly account for the greater percentage of failure to obtain adequate information. Blocked vessels or other roentgen findings account for additional failures.

ZION.

O'Loughlin, B. J.: Roentgen Visualization of the Inferior Vena Cava. *Am. J. Roentgenol.* 58:617 (Nov.), 1947.

The author outlines a simple and safe procedure for visualizing the inferior vena cava. No serious ill effects were encountered in fifty consecutive cases. The patient is prepared in a manner similar to that used in intravenous urography. Sphygmomanometer cuffs are placed about the thighs as proximal as possible, leaving room for femoral venepuncture. The pressure in the cuffs is adjusted to diastolic pressure or slightly higher. Twenty cubic centimeters of a 35 per cent Diodrast solution are injected through a 18 gauge needle on the side selected. The rate of injection is approximately 1.0 c.c. per second. The usual kidney-ureter-bladder exposures are made outlining the common iliac veins and inferior vena cava. Having the patient hold his breath during the exposure and injection tends to make the blood column move more slowly and smoothly. A Valsalva effort may reverse the flow sufficiently to outline the branches of the iliac veins. The removal of the cuffs releases the dammed-up venous blood from the lower extremities and may wash out or dilute the slightly thrombogenic influence of the Diodrast.

ZION.

L'Farinas, P.: Abdominal Venography. *Am. J. Roentgenol.* 58:599 (Nov.), 1947.

The author described a technique of abdominal venography. Under local anesthesia the long saphenous vein is exposed by a small incision at the inner portion of the middle third of the thigh. A tourniquet at the groin permits better visualization of the vein which is then punctured with a small trocar. The tourniquet is released and 40 c.c. of Diodrast is rapidly injected into the vein. Two 14 by 17 inch film exposures of the abdomen are made. The first was made when 20 to 25 c.c. of the opaque material has been injected and the second immediately after the completion of the injection. Normal venography visualizes the femoral, external, common iliac veins, and the inferior vena cava. Compression of the epigastric region with an inflated balloon may permit visualization of the renal, hepatic, and internal iliac veins.

Indications for abdominal venography are: (1) obstruction or thrombosis of the inferior vena cava; (2) abdominal tumors, especially renal neoplasms where intravenous urography is indicated; (3) liver conditions that lead to portal hypertension with the possibility of a portal vein-vena cava anastomosis in order to determine the integrity of the vena cava.

In thrombophlebitis the site of obstruction of the vessels can easily be demonstrated. In tumors that compress and displace the inferior vena cava and common iliac veins, the site of compression and displacement together with the establishment of collateral circulation can be demonstrated.

ZION.

White, P. D.: The Management of Hypertension. *Ann. Int. Med.* 27:740 (Nov.), 1947.

This is a brief review of therapeutic methods which have proved to be of some value in the management of hypertension. There is a short summary of the value of education of the patient concerning the true meaning of an elevated blood pressure and of the effectiveness of vacations, a regulated mode of living, mental relaxation, physiotherapy, and intensive psychotherapy. The importance of restriction of tobacco, coffee, and tea is stressed. The use of the low-salt diet or the strict rice diet is looked upon favorably. Aside from the sedation accomplished by

bromides or phenobarbital, drugs seem to occupy a small place in the management of hypertension. It is too early to decide upon the merits of the newer sympatheticolytic drugs, such as tetraethyl ammonium and Priscol. Of the surgical approaches, the extensive lumbodorsal sympathectomy advocated by Smithwick has proved to be worth while in about 75 per cent of the properly selected cases:

WENDKOS.

Ray, C. T., and Burch, G.: Vascular Responses in Man to Ligation of the Inferior Vena Cava. Arch. Int. Med. 80:587 (Nov.), 1947.

The authors investigated the circulatory adjustments in twelve patients following ligation of the inferior vena cava in the treatment of pelvic thrombophlebitis. In all instances but one, there was an elevation in venous pressure in the lower extremities and a gradual decline toward normal in the subsequent years of observation. A tendency for the plasma protein content to increase was also noted after ligation.

With regard to clinical observations, no diminution in functional capacity was observed, nor was any intermittent claudication experienced. The severity of the edema varied from mild to extreme, disappearing within two months after operation in all cases but three. For the most part, the large veins of the legs and feet were not dilated, and no demonstrable varicosities were noted. Some small varicosities were present in the cutaneous veins. The superficial veins of the abdominal wall and gluteal region and also the long thoracic veins were dilated, forming an unusually prominent network.

The authors concluded that remarkable readjustments occur in the lower extremities after ligation of the inferior vena cava. The fact that the edema disappeared at a time when the venous pressure in the lower extremities was still considerably elevated appeared to support the view that hydrostatic intravascular pressure, per se, plays a relatively unimportant role in edema formation, and that as long as only the hydrostatic pressure is increased, compensatory mechanisms develop to a high degree.

ABRAMSON.

Magner, D., and McKenzie, H. F.: Cystic Medionecrosis of the Aorta. Arch. Path. 44:485 (Nov.), 1947.

The authors report a case of large, fusiform aneurysm of the ascending arch of the aorta in a 23-year-old man in whom death occurred as a result of perforation into the pericardial sac with resulting tamponade of the heart. The patient, first seen two years previously because routine x-ray examination revealed a large mediastinal mass, had had no relevant past medical history, except that at the age of 18 years, after playing hockey, he had had severe retrosternal pain for three days. There was no traumatic incident. Repeated x-ray examinations showed a gradual increase in the size of the mediastinal mass, which was seen to pulsate in the fluoroscopic examination. Serologic tests were negative and the patient worked in good health for three years following the initial discovery of the aneurysm.

A few days after a bronchoscopy which showed pulsation in the trachea, the patient collapsed and died with a perforation of the aneurysm into the pericardium. Unfortunately, no blood pressure record was obtained. Laboratory data revealed nothing of note.

At necropsy the heart was found to be of normal weight and showed no abnormality. The aortic valve leaflets were described as normal, despite the close proximity of the aneurysm, which involved the ascending and transverse portion of the arch. Detailed histologic examination revealed characteristic changes of cystic medionecrosis and excluded syphilis as an etiological factor. The authors comment on the complete lack of knowledge of the origin of this lesion.

GOULEY.

Kobernick, S. D.: Gumma of the Coronary Artery, Myocardial Infarction and Gumma of the Heart. Arch. Path. 44:490 (Nov.), 1947.

The author presents the first recorded case of myocardial infarction due to coronary thrombosis secondary to syphilitic gummatous coronary arteritis. He emphasizes the generally known fact that syphilitic aortitis often narrows and sometimes closes the coronary orifices, and that syphilitic coronary arteritis seldom involves more than the first centimeter of the two main arteries.

This unique case was that of a 44-year-old white man, serologically positive, with signs of aortic regurgitation, who was hospitalized because of severe epigastric pain accompanied by sweating. The heart sounds became distant and a gallop rhythm was present. The electrocardiogram showed evidence of an acute posterior myocardial infarction. Death occurred on the day after admission.

Autopsy revealed an enlarged heart with hypertrophy of the left ventricle associated with syphilitic aortitis and aortic regurgitation. Multiple aneurysms were noted in the aortic arch. Gummatous masses were found in the pulmonary conus and the pulmonary artery. A necrotic degeneration in the upper portion of the posterior wall of the left ventricle which extended into the adjacent ventricular septum was microscopically a myocardial infarction. Examination of the nutrient artery, namely, the right coronary, showed marked narrowing beyond its orifice for 2.0 cm. by eccentric grey-white thickening of the vessel wall. The narrowed lumen was completely blocked with red-brown thrombus. Microscopically the arterial thickening was found to be a gumma, involving the adventitia and the media, and extending into the intima. The accompanying photomicrograph shows a typical coagulative necrosis (gumma) involving the entire thickness of the wall of the right coronary artery.

GOULEY.

Wagner, F. B., Price, A. H., and Swenson, P. C.: Abdominal Arteriography. Am. J. Roentgenol. 58:591 (Nov.), 1947.

The patient is prepared by enemata in the morning of the examination and food is withheld. Preanesthesia medication of morphine and atropine is given forty-five minutes before the procedure. A preliminary exposure of the abdomen is made to check proper cleansing of the colon and correctness of the exposure factors. The patient is lightly anesthetized with 2.5 per cent pentothal sodium solution. A second anesthetist administers oxygen from a gas machine.

A special aortic puncture needle, 18 gauge and at least 15 cm. in length (malleable needle), is used. Antiseptic preparation of the back is done in the usual manner. The skin is pierced just below the left twelfth rib, four fingerbreadths from the spinous process. The needle is directed anteriorly, medially, and cephalically toward the body of the twelfth vertebra until bone is encountered. The needle is then withdrawn 2.0 cm. and the point directed more laterally so as just to slip by the body of the vertebra. The stylet is removed and the needle advanced cautiously into the aortic lumen. (When the aorta is pierced there is a sensation similar to that encountered in piercing the dura in spinal puncture.) After the needle has entered the aorta it is advanced an additional 0.5 centimeter. A pulsating drip of bright red blood rather than spurting is encountered. The needle is connected to two feet of rubber tubing and a Luer-lock syringe. Alternating injection of saline and withdrawal of blood are performed in order to assure proper function of apparatus and correct position.

A trial injection of 12 c.c. of saline solution is performed. If the test is satisfactory, 12 c.c. of 80 per cent sodium iodide solution is injected at the rate of 2.0 c.c. per second. The roentgen exposure is made as the last 1 to 2 c.c. are leaving the syringe. The needle is immediately withdrawn following the exposure.

The sodium iodide is freshly prepared and sterilized the day preceding the examination. A 70 per cent Diodrast solution has proved to be unsatisfactory. Following the examinations, one liter of 5 per cent glucose in normal saline solution is administered through the intravenous anesthesia needle. After two hours the patient is allowed a regular diet and walking is permitted if there are no other contraindications. No untoward reactions have occurred in a series of twenty-six cases.

For visualization of the celiac axis and branches, puncture is best performed at the twelfth dorsal vertebra. For visualization of the renal vessels, aortic puncture should be made one vertebra lower. For the iliac vessels and branches, puncture may be performed at the level of the second or third lumbar vertebra. Puncture at the lower levels is more difficult and it is necessary to enter the skin at six fingerbreadths from the spinous process.

Aneurysms and aortic occlusions are well demonstrated by this procedure. The method also lends itself to excellent visualization of the iliac and femoral arteries. Abdominal aortography is also of value in the diagnosis of certain abdominal tumors, particularly retroperitoneal masses of renal or adrenal origin.

ZION.

Katz, L. N.: A Survey of Recent Developments Concerning the Concepts of Coronary Disease and Its Management. *Ann. Int. Med.* 27:705 (Nov.), 1947.

The prognosis and management of coronary insufficiency depend on a knowledge of the natural history of coronary disease and of the factors involved in the control of the coronary circulation. Coronary sclerosis leads to ill effects by handicapping the adjustments of coronary vessels to the needs of the heart for varying amounts of blood flow. There are compensatory blood channels (the intercoronary communications, arteriovenous anastomoses, Thebesian vessels, and extracardiac collaterals) which enlarge and take over the supply of blood to the region whose coronary artery is occluded or narrowed. The adequacy of this auxiliary blood supply depends most of all upon the rapidity of the narrowing of the coronary arteries.

Age is of some importance because the coronary arteries are more nearly end arteries functionally in the young than in the old in whom these auxiliary channels have had time to develop. In the present state of our knowledge, it is not yet justified to advocate a cholesterol-poor diet in man in the hope of retarding atherosclerosis because there is reason to believe that endogenous cholesterol produced even on a cholesterol-poor diet may still lead to atherosclerosis.

Other factors besides the architecture of the coronary vessels are involved in determining the adequacy of coronary flow. It is for this reason that the term coronary insufficiency to express an inadequate coronary flow has been created and has gained wide vogue recently. The dynamic or physiologic concept serves a useful purpose in that it permits the clinician to judge whether the coronary system is able to nourish the heart adequately. Coronary insufficiency, therefore, is really to be expressed in terms of relative insufficiency. Coronary insufficiency may be focal or generalized, transitory or protracted. The transitory and the protracted forms of coronary insufficiency are often superimposed upon chronic coronary insufficiency and may be the terminal event. Focal coronary insufficiency is more likely to lead to myocardial infarction, while generalized insufficiency is more likely to lead to chronic or acute heart failure.

Except in the subendocardial layers of the ventricular myocardium, coronary blood flow is increased during the phase of cardiac systole. There is also a direct relationship between coronary flow and the cardiac output. This relationship is unaffected by the change in blood pressure. The role of vasomotor influences in altering the caliber of the coronary vessels is also discussed, and the author makes a special point of emphasizing that the vagus nerve is not a coronary constrictor but rather a coronary dilator. It is his opinion that vasoconstriction of neurogenic origin results from sympathetic overstimulation and not vagal overactivity. For this reason he questions the value of atropine sulfate in the treatment of acute myocardial infarction or acute pulmonary embolism. The author refers to experimental work which indicates that the nitrites and papaverine are the most powerful coronary dilators, whereas xanthines are very much weaker. He also observes that potassium in large doses, Pitressin, and foreign species of blood are powerful vasoconstrictors. The significance of electrocardiographic changes which follow a standard exercise test in so far as it relates to the diagnosis of coronary insufficiency is briefly discussed. The factors and mechanisms responsible for pain in coronary artery disease are amply reviewed, and the importance of such knowledge in relation to the diagnosis of coronary artery disease is emphasized. In the discussion concerning prognosis, it is pointed out that about one-fifth of the patients with recent myocardial infarction died during their hospital stay; that the average expectancy of life following an infarct is five years, but that the scatter is quite large and some

patients have lived very comfortably for over twenty years following an infarction. The factors which determine the prognosis in recent myocardial infarction and in other forms of coronary artery disease are admitted to be still poorly understood and, therefore, make it impossible to prognosticate accurately in any given patient. It is pointed out that those patients who develop a marked drop in blood pressure or go into shock have a poor prognosis and that the development of congestive heart failure or the presence of diabetes adds to the gravity of the outlook. The author recognizes that many people have had infarcts without any symptoms, without any special medical care, and the evidence of this was written in their hearts and revealed at necropsy sometime later when they died of some other circumstance or of a new infarction. He concludes that infarction is statistically more benign than is generally appreciated, that it is a self-limited disease, and that it is a process which by the time the clinician sees the case, is already a matter of convalescence, that four of five patients will survive the episode, and that most of them will have little if any handicap. Some will develop chronic coronary insufficiency, but others will be completely restored and will have, at most, only the psychological fear that all lay people and too many physicians attach to coronary episodes. In the concluding portion of the paper, there is a lengthy discussion based on modern physiologic concepts, concerning the treatment of patients with the manifestations of acute and chronic coronary insufficiency.

WENDKOS.

Rich, A. R., and Gregory, J. E.: Experimental Anaphylactic Lesions of the Coronary Arteries of the "Sclerotic" Type, Commonly Associated With Rheumatic Fever and Disseminated Lupus Erythematosus. Bull. Johns Hopkins Hosp., 81:312 (Nov.), 1947.

Forty-five rabbits were sensitized to horse serum in a manner known to be favorable to the production of the serum sickness type of protected anaphylactic reaction both in man and rabbit, namely, the intravenous injection of large amounts of the antigen. A group of eighteen male albino rabbits, weighing approximately 200 grams each, were kept as controls. Male albino rabbits, averaging about 2 kilograms in weight were used in the experiments. Sterile horse serum without preservative was injected into the ear vein in a dosage of 10 c.c. to 15 c.c. per kilogram. Seven of the forty-five animals received only a single injection; twenty-five received two injections; and thirteen received five to ten injections at various intervals. The animals were killed at periods between 17 and 364 days following the first injection of serum, and the coronary arteries were studied in appropriate sections of the heart.

All of the animals in which lesions of the coronary arteries were found at autopsy had developed the serum sickness type of reaction (fever, erythema) following one or more of the intravenous injections of serum, but arterial lesions were not found in all animals which had exhibited this type of reaction. Eighteen of the forty-five sensitized rabbits developed lesions of the coronary arteries of the type familiar in rheumatic fever. Three of the eighteen that developed the coronary lesions had received only one injection of horse serum; thirteen had received two injections; one had received five, and one nine injections. No lesions of the coronary arteries were found in any of the control animals. Fibrotic intimal lesions, similar to those occurring in the coronary arteries, were found in peripheral arteries of some of the sensitized animals.

These authors make the point that the same type of "sclerotic" lesions of the coronary arteries which are observed in disseminated lupus erythematosus, in rheumatic fever, and in periarteritis nodosa were also found in the animals subjected to experimental serum sickness.

BELLET.

Ruzicka, E. R., and Nicholson, M. J.: Cardiac Arrest Under Anesthesia, J.A.M.A. 135:622 (Nov. 8), 1947.

In the past five years the authors studied nine cases of cardiac arrest, which occurred under anesthesia. The following factors were considered to be of etiological significance in the production of cardiac arrest: The ability of cyclopropane, chloroform, and ethyl chloride to sensitize the heart to epinephrine; excitement also causes an outpouring of epinephrine into the circulation; barbiturates given intravenously and cyclopropane exhibit a parasympathetic effect on

the heart; stimulation of the vagus nerve may cause a powerful inhibitory effect on the heart. It is likely that one or more of the aforementioned factors is present in every instance of sudden cardiac arrest during anesthesia. The authors point out that treatment to be effective must begin within three to five minutes after cardiac arrest. They present the following plan of action: (1) The anesthesiologist must immediately begin artificial respiration with 100 per cent oxygen. (2) The surgeon must begin cardiac massage immediately. (3) Drug therapy consists of the use of two drugs: procaine and epinephrine. (4) General methods of treatment include the intravenous administration of fluids and the institution of 5 to 10 degrees of Trendelenburg position.

In the authors' series of nine cases the heart was revived in every instance. There were three complete recoveries and one apparent recovery but with death of the patient on the second postoperative day from acute cardiac failure. Although cardiac activity was resumed in the remaining five cases, none of the patients regained consciousness. Ventricular fibrillation is reported to be the most frequent complication occurring in cardiac resuscitation, and is fatal unless quickly corrected. This is first attempted by cardiac massage; another method is by electrical countershock. Death often occurs during the period of one to fifteen days after operation. During this time these patients show every evidence of damage to the brain. Many times the gross pathologic changes are the result of rough or forceful cardiac massage. Those patients who recover have a constant loss of memory for events twenty-four hours previous to operation. The repeated incidence of normal survival appears to be 10 per cent or less in cases of cardiac arrest. The normal survival rate in the author's experience is approximately 33.33 per cent.

BELLET.

Shumacker, H. B. J.: Surgical Cure of Innominate Aneurysm: Report of a Case With Comments on the Applicability of Surgical Measures. Surgery 22:729 (Nov.), 1947.

This author found in the literature reports of thirty-seven attempts on direct operative attack on aneurysms of the innominate artery. Only nineteen patients survived and not all of them have been cured. There are several difficult aspects to the surgical management of this lesion, one of the most serious being the matter of exposure. Shumacker employed a sternum-splitting incision, supplemented by subperiosteal resection of the medial third of the right clavicle, which allowed excellent visualization of the aneurysm and the great vessels.

The ideal treatment of proximal and distal ligation of the main artery with excision or obliteration of the sac has been accomplished in three cases. The next procedure of value, which was employed in four cases, is ligation of the proximal artery (innominate) and distal arteries (subclavian and carotid) which is somewhat less hazardous to carry out. Of the seven patients, six were cured and one died eight years later, of recurrence and hemorrhage due to rupture.

There are several important points in the management of these cases: (1) in order to lessen the danger of a cerebral complication, repeated testing of the patient's ability to withstand prolonged carotid compression is valuable. (2) Although no incident of gangrene of the hand has been observed, the author noted that in his case temporary complete occlusion of the innominate artery resulted in a cold, pale, apparently bloodless hand. For that reason he partially occluded the innominate artery with a strip of fascia, and a band of cellophane was wrapped around the vessel. An upper thoracic sympathectomy was performed six weeks later which improved further the collateral circulation to the right hand. Because the bruit returned in full and the oscillometric reading in the right arm returned to a normal level, it was felt that the band around the artery had given way. Therefore, three and one-half months after the first procedure, Schumacker again opened the mediastinum and carried out proximal ligation of the innominate artery and distal ligation of the subclavian and common carotid arteries. The innominate, jugular, and subclavian veins were also ligated and excised. The aneurysmal sac was opened and the laminated thrombus was removed. The patient has remained entirely well for eighteen months with only slight fatigability and weakness of his right hand.

LORD.

Cooper, F. W., Jr., Robertson, R. L., and Dennis, E. W.: The Use of Tetraethylammonium Chloride in the Treatment of Experimental Acute Arterial Insufficiency. *Surgery* 22:740 (Nov.), 1947.

The authors carried out resection of the distal aorta including the common iliac arteries and the deep circumflex iliac vessels in thirty dogs. In the control group of ten dogs, nine of the animals died within seven days of the operation. Autopsy showed that death was not due to hemorrhage or peritonitis. All of the animals experienced hindlimb paralysis, coldness, cyanosis, and varying degrees of swelling. In the group of twenty dogs treated with tetraethylammonium chloride, fourteen of the animals survived. These animals regained excellent functional activity within two to six days. Three of the six dogs which died had as their cause of death infection of a posterior extremity. One of the remaining animals died within twelve hours of the operation.

The tetraethylammonium chloride was administered intramuscularly, in doses of 25 mg. per kilogram of body weight immediately after excision of the arteries and was continued post-operatively at eight-hour intervals for three days.

The authors conclude that sympathetic interruption following an acute arterial injury is a valuable procedure and that tetraethylammonium chloride may be of value either as a substitute for other methods of sympathetic interruption or as a preliminary to them.

LORD.

Davis, H. A., and King, L. D.: A Comparative Study of Thromboangiitis Obliterans in White and Negro Patients. *Surg., Gynec. & Obst.* 85:597 (Nov.), 1947.

The authors reviewed the literature with regard to the presence of thromboangiitis obliterans in the Negro race and pointed out that in only one of the ten reported cases could the patient be considered to be a full-blooded Negro. In their own series of sixty-four cases of thromboangiitis obliterans, nine were Negroes and in four of these pathologic examination verified the clinical diagnosis. However, it was established in at least one of them, a woman, that she was not a full-blooded Negro. With regard to the others, this point was evidently not investigated. The authors found that nonsurgical treatment was conspicuously less successful in Negro than in white patients.

ABRAMSON.

Gold, Harry, Kwit, N. T., Modell, W., Hanlon, L. W., Kramer, M., Greenberg, S., Otto, H. L., Cotlove, E. W., Benton, J. G., Pearlmutter, M., and Zahn, W.: A System for the Routine Treatment of the Failing Heart. *Am. J. Med.* 3:665 (Dec.), 1947.

The authors propose a standardized regimen for the treatment of cardiac failure. It involves five cardinal factors: the simultaneous use of the mercurial diuretics, salt restriction, abundant water, digitoxin, and the charting of the course by a record of the body weight.

The patient is put at rest, given a diet consisting of four to six glasses of milk daily plus a water intake of two to three quarts. If no digitalis has been taken recently, 1.2 mg. of digitoxin are given at one time followed by 0.2 mg. daily as a maintenance dose. A daily weight record is kept. Mercuhydrin is given daily, beginning with a dose of .5 c.c. and increasing to as high as 2 c.c. daily. This regimen is continued until all signs of failure disappear and the weight declines to a resistant level, the "dry weight."

Maintenance is guided by the daily weight, and Mercuhydrin dosage determined accordingly. The patients or their families are taught to administer the latter. A more liberal diet is usually allowed but it is low in salt.

Each factor of the regimen is discussed in detail, as well as guides to treatment, maintenance programs, and unpleasant symptoms.

The authors state that the present study, comparing the results in 502 admissions for congestive failure with results in 140 similar admissions treated by the proposed system, shows that the symptoms and signs of congestive failure subside in about 90 per cent of hospital admissions when this system is employed routinely, against about 50 per cent with the current methods in common use; and that the duration of required hospital stay is reduced to about one-third of the time necessary

to bring about similar results by the current methods of treatment. They further state that only two types of results are obtained with the proposed method, namely, a few failures and the rest complete recoveries.

WOODS.

Friedman, M., and Binc, R., Jr.: Observations Concerning the Influence of Potassium Upon the Action of a Digitalis Glycoside (Lanatoside C). *Am. J. M. Sc.* 214:633 (Dec.), 1947.

Although there is experimental and clinical evidence to support the theory that potassium in physiologic excess tends to inhibit the action of digitalis, there is little known about the physiologic inter-relationships of the two substances. This study, therefore, was concerned with the effects of different concentrations of potassium upon the normal embryonic duck heart. It was found that the absence of potassium led to arrhythmias and early cessation of beating. Excess potassium, conversely, depressed heart action. The absence of potassium was found to enhance the effects of a digitalis glycoside (lanatoside C), whereas an excess of potassium inhibited the actions of the same drug. Only large or toxic amounts of digitalis glycoside were found to cause a probable loss of potassium from the heart. Excess potassium was effective in inhibiting this process.

The results of the entire study indicated that excess potassium was able to inhibit the actions of digitalis glycoside (1) by depressing the irritability of the heart, and (2) by serving as a source of potassium to a heart apparently losing it after exposure to toxic amounts of digitalis.

DURANT.

Stepman, T. R., and Owyang, E.: Clinically Primary Tuberculous Pericarditis. *Ann. Int. Med.* 27:914 (Dec.), 1947.

Three men, aged 60, 42, and 30 years, respectively, died following a protracted febrile illness during which a pericarditis with effusion was a prominent feature of the disease. In the first two patients, chronic pulmonary tuberculosis was not present and disseminated miliary tuberculosis was the terminal event. In the third patient, there were tuberculous excavative lesions in the lungs and a tuberculous enteritis with ascites. Pericardial paracentesis was performed in each patient during life, but in only one was the tubercle bacillus recovered from the pericardial fluid. At necropsy, a thickened adherent pericardium was noted in each instance.

WENDKOS.

LaDue, J. S., and Carter, S. B.: The Efficacy of Maintenance Doses of Digitalis in Preventing the Recurrence of Congestive Heart Failure. *Ann. Int. Med.* 27:923 (Dec.), 1947.

One hundred four patients with heart disease associated with regular sinus rhythm who had been discharged from the hospital wards after treatment for congestive heart failure were followed at intervals of from one to four weeks over a period of from six months to two years. At the time the study was begun, most of the patients had been taking 0.1 to 0.3 Gm. of digitalis leaf per day for several weeks or months after discharge from the hospital. Measurements of venous pressure, circulation time, vital capacity, and weight were made during a one-to three-month period at intervals from one to four weeks; then digitalis was discontinued and the same measurements repeated at the same intervals of time. The degree of dyspnea, orthopnea, and edema was recorded, as well as the presence or absence of râles, the size of the liver, the cardiac findings, and the subjective state of the patient.

The data were broken down according to the variation in the measurements of the venous pressure, circulation time, vital capacity, weight, heart size, and frequency of the development of congestive heart failure while the patients were being studied. In general, it can be stated that none of the criteria employed for measurement of the circulation revealed any significant differences during the time digitalis was given to the patient and during the period that the drug was withheld. Patients with heart disease who were not in failure had on the average, lower vital capacity and longer circulation time measurements than did normal individuals of the same age

group. Changes in weight appeared to be just as sensitive as the level of the venous pressure, circulation time, or vital capacity in evaluation of the presence or approach of congestive heart failure. With the possible exception of changes in vital capacity and weight, detailed questioning of the patient with regard to dyspnea, orthopnea, and transient ankle edema, together with a careful physical examination, were more reliable in evaluating the state of the circulation than repeated measurements of the circulation time, venous pressure, or heart size.

It was noted that maintenance doses of digitalis leaf given to patients who had congestive heart failure failed to produce permanent and significant changes in diastolic heart volume once compensation was established. It was also observed that twice as many patients developed congestive heart failure during the period without digitalis than did those who were maintained on adequate doses of the drug.

Finally, the authors suggest that frequent re-evaluation of the therapeutic level of digitalization is indicated in patients who have at one time in the past developed congestive heart failure.

WENDKOS.

Tarr, L.: Effect of the Antimony Compounds, Fuadin and Tartar Emetic, on the Electrocardiogram of Man; A Study of the Changes Encountered in 141 Patients Treated for Schistosomiasis. Ann. Int. Med. 27:970 (Dec.) 1947.

Serial electrocardiograms were made in 141 patients who were treated with Fuadin and/or tartar emetic because of infestation with *Schistosoma japonicum*. Every patient receiving a course of tartar emetic showed some degree of T-wave alteration in the electrocardiogram, varying from slight depression to deep inversion, whereas in those receiving Fuadin, comparable alterations occurred in 57 to 80 per cent of the patients. In 30 per cent of the entire number, the magnitude of the abnormality was of a high order, whereas only 6 to 14 per cent of the Fuadin-treated group showed such marked changes. In none of these patients did associated S-T segment deviations occur. Although the quantitative change in the electrocardiogram in the tartar emetic and Fuadin-treated groups was different, qualitatively, the alterations encountered were identical. A striking feature was the reversible nature of the changes. In 90 per cent of those whose electrocardiograms showed varying degrees of T-wave change following either small or large doses of Fuadin or tartar emetic, these deflections returned to normal in thirty to sixty days after cessation of treatments. No correlation should be established between the amount of the drug which had been administered and the degree of T-wave change which developed.

Fuadin is a sodium compound of trivalent antimony and tartar emetic is a potassium compound of trivalent antimony. Since the electrocardiographic changes following potassium administration are entirely different from those observed, and since the alterations following the administration of these two drugs were similar, the potassium ion was not considered a possible factor responsible for the modification of the T wave. A vagal origin was seemingly excluded because the abnormalities were not influenced by a tropine sulfate. However, the amount of atropine sulfate which was used was inadequate to permit any valid conclusion in this regard. The author considers that the T-wave alterations are the result of a temporary deposition of antimony in the heart muscle which, in turn, alters the electrical activity of the ventricle. The disappearance of the T-wave changes, therefore, is considered to be the result of excretions of this metal from the heart muscle.

WENDKOS.

Gibson, J. G., II, Seligman, A. M., Peacock, W. C., Fine, J., Aub, J. C., and Evans, R. D.: The Circulating Red and Plasma Volume and the Distribution of Blood in Large and Minute Vessels in Experimental Shock in Dogs, Measured by Radioactive Isotopes of Iron and Iodine. J. Clin. Investigation 26:126 (Jan.), 1947.

Normal dogs under morphine narcosis or Nembutal anesthesia were subjected to a variety of procedures designed to induce various degrees of shock. Measurement of the circulating blood volume in animals shocked by hemorrhage revealed a greater reduction in the volume of circulating cells and plasma than could be accounted for by known *external* blood loss. By special techniques

it was found that this discrepancy was due to *trapping* of blood within the minute vessels of all the organs in the body and further, that the erythrocytes removed from the *effective* circulation within the minute vessels represented a very large percentage of the total quantity of erythrocytes normally circulating within these vessels. This phenomenon of trapping was observed regardless of the nature of the shocking procedure, e.g., burns, muscle trauma, hemorrhage, or administration of bacterial toxins.

Although the degree of trapping bore no relationship to percentile reduction in total blood volume, it did appear to be roughly related to the decline in arterial pressure, in that the ratio of circulating to total red cells in minute vessels was 0.8 or less in dogs whose mean arterial pressures fell more than 65 mm. Hg, whereas ratios higher than 0.8 were accompanied by pressure drops of less than 30 mm. of mercury.

In one series of experiments, infusions of bovine albumin were given and resulted in an immediate rise in mean arterial pressure in most shocked animals. Infused animals in which the circulating red cell volume displayed no upward trend had only a temporary rise in arterial pressure and eventually succumbed; others in which the circulating red cell volume increased following infusion maintained their arterial pressures and survived.

These experiments indicate that the treatment of shock should be directed not only toward the restoration of blood volume but also toward *circulating* red cell volume in order that trapped erythrocytes be flushed back into the circulation.

FRIEDLAND.

Houston, C. S., and Riley, R. L.: Respiratory and Circulatory Changes During Acclimatization To High Altitude. Am. J. Physiol. 149:565 (June), 1947.

Detailed studies of the respiratory and circulatory changes which occur during the process of acclimatization to oxygen lack were made on four men exposed to gradually increasing simulated altitude during one month in a low pressure chamber. The data strengthen the concept that acclimatization consists of a series of integrated adaptations which tend to restore the oxygen pressure of the tissues toward normal sea level values despite the lowered pO_2 of the atmosphere.

The same pulmonary and circulatory changes which caused an increase in pO_2 as acclimatization progress necessarily caused a decrease in pCO_2 ; and an initial effect of the decrease in pCO_2 was an increase in the alkalinity of the blood. As acclimatization progressed, further changes occurred to counteract this respiratory alkalosis. The fall in blood bicarbonate reflected the extent of these changes which included a net increase in the other negative ions and probably a net decrease in the positive ions.

There is no evidence that cellular metabolism decreased as part of the acclimatization process, since the oxygen consumption remained the same at simulated high altitude as at sea level, both during rest and work. Since clinical evidence indicated that the subjects were moderately anoxic, it appears that cellular function was impaired by low pO_2 even though the amount of oxygen used by the cells remained normal.

BERNSTEIN.

Altschule, M. D., and Rosenfeld, F. M.: Increased Catabolism Following Acute Myocardial Infarction. Arch. Int. Med. 80:74 (July), 1947.

Three patients with myocardial infarction in whom persistent shock did not occur were studied and they all showed evidences of a preponderance of catabolic activity. The daily nitrogen loss averaged 4.4 to 8.1 Gm. per day as compared with an average daily loss of 0.38 to 0.58 Gm. per day in a control group. The authors presume the rise in nonprotein nitrogen which frequently occurs following myocardial infarction is probably the result of increased delivery of nitrogen to the kidneys consequent to increased protein catabolism at a time when renal function may be decreased as a consequence of vasoconstriction or, in some cases, shock. The elevation of blood lactate and pyruvate are also probably a consequence of increased destruction of body protein and increased catabolism in general. Myocardial infarction is compared to severe thyrotoxicosis, thermal burns,

and prolonged high artificial fevers as being characterized by a negative nitrogen balance, hyperglycemia, elevated blood lactate and pyruvate, and not infrequently, an unexplained hyperbilirubinemia.

BERNSTEIN.

Rosenkrantz, J. A., and Marshal, C.: Basal Metabolic Rate in Hypertensive Vascular Disease. Arch. Int. Med. 80:81 (July), 1947.

In hypertensive vascular disease without cardiac insufficiency (determined by checking the electrocardiogram 6-foot silhouette, and the physical condition), a significant incidence of hypermetabolism has been demonstrated, in that there is a decided positive correlation between basal metabolic rate and both systolic and diastolic blood pressure. On the other hand, there appears to be no significant association between basal heat production and pulse pressure. Further analysis revealed a greater incidence of renal dysfunction in hypertensive patients with increased basal metabolic rates than in those with normal or subnormal basal heat production, perhaps because of the fact that those with renal dysfunction had a greater elevation in blood pressure. The possibility that thoracolumbar sympathectomy can lower basal metabolic rates may explain one of the mechanisms producing elevated rates in some hypertensive patients. In this study, thoracolumbar sympathectomy resulted in a reduction of basal heat production without an appreciable alteration of blood pressure. One must consider that cardiac work may be a factor in elevating metabolic rate since a direct correlation between basal metabolic rates and blood pressure, as well as a greater incidence of renal dysfunction was found in this series of hypertensive patients with elevated metabolic rates.

BERNSTEIN.

Stead, E. A., Jr., and Warren, J. V.: Cardiac Output in Man. Arch. Int. Med. 80:237 (Aug.), 1947.

This paper attempts to present new data in an effort to throw light on the mechanisms controlling the cardiac output in man, a subject which current medical teaching admits is based mainly on the concepts of animal physiology. The cardiac output was determined by the direct Fick principle or the ballistocardiograph. It was found that the ventricles play an active rather than a passive role in determining the cardiac output, in that the cardiac output is varied by changes in ventricular relaxation and contraction which are independent of fairly wide variations in atrial pressure. Lowering the arterial pressure causes an abrupt rise in cardiac output which occurs too rapidly for a humoral mechanism. Anxiety and exercise increase output even in the presence of an increase in arterial pressure.

It is suggested that reflex stimulation of ventricular activity accounts for the changes in cardiac output during daily activity and the afferent stimuli may arise in part from a lowering of the arterial pressure, movement of limbs during exercise, and the emotional content of thought. Clinical observations which support the concept that the cardiac output is under reflex control are discussed.

BERNSTEIN.

Smith, J. A., and Levine, S. A.: Aortic Stenosis With Elevated Metabolic Rate Simulating Hyperthyroidism. Arch. Int. Med. 80:265 (Aug.), 1947.

The authors report a series of four cases of aortic stenosis without dyspnea or significant pulmonary congestion in which the patients showed definite and persistent elevated basal metabolic rates (34 to 53 per cent) and had normal thyroid glands grossly and microscopically. In view of the fact that these patients also manifested some other feature suggestive of thyrotoxicosis, the authors suggest that we add this group of patients to the group of conditions that need to be considered in the differential diagnosis of masked thyrocardiac disease; that is, cardiac failure, hypertension, per se, polycythemia, coarctation of the aorta, and cardiac failure associated with beriberi.

BERNSTEIN.

Book Reviews

VARICES SU TRATAMIENTO BASADO EN LA FLEBOGRAFIA. By Dr. F. Martorell, Barcelona, Spain, 1946, Teleres Graficas Ibero-Americanos, 140 pages, 118 figures.

This book by Dr. F. Martorell, Chief of the Vascular Surgery Division of the Polyclinic Institute of Barcelona, is an exhaustive attempt at a precise diagnosis of the varicosities of the lower extremities by phlebography. The author devotes two chapters to the elemental facts of the venous circulation in the lower extremities. The differential diagnosis of varices is contained in the second part of the book. The Trendelenburg phenomenon, Perthes, Ochsner and Mahorner, and Pratt tests are discussed and compared with the author's own method. The other methods are too inexact, and this is the reason why Dr. Martorell has developed phlebograms to such a high degree of efficiency. An exact visualization of the insufficient communicating veins gives the localization for ligation, shortens the operation, avoids useless and dangerous ligations, and permits ambulatory treatment of all patients, thus minimizing the chance of embolization. The book is amply illustrated with diagrams and photographs. It deserves study in the English speaking medical world.

BERNARD E. NUNEZ, M.D.

TENSION ARTERIAL Y BIOTIPO. By F. Schaposnik, Buenos Aires, 1947, El Ateneo, 120 pages, 27 charts.

The author studied the possible correlation between arterial blood pressure and physical constitution. Seven hundred nine persons of both sexes between 14 and 22 years of age were studied.

The macrosplanchnic type showed the greatest percentage of readings above 140 mm. Hg systolic, while the normosplanchnic type presented such readings more often than the microsplanchnic. Tall persons usually have a higher blood pressure than persons of average height, but smaller individuals may also have higher than normal figures.

The microsplanchnic type presents a lower diastolic pressure than the normal type while the macrosplanchnic type presents a higher diastolic pressure than the normal.

Pulse pressure was larger in macrosplanchnic men and in normal women than in the other types.

In conclusion, a definite relationship between body structure and blood pressure is suggested, even if the difference between the observed figures is not striking.

A. LUISADA, M.D.

DERIVACÖES UNIPOLARES DAS EXTREMIDADES CONTRIBUICÃO AO ESTUDO DOS SEUS ASPECTOS NORMAIS. By Horácio Kneese de Melo, Sao Paulo, 1947, Indústria Grafica Siqueria, 78 pages and 15 figures.

This seventy-eight page monograph by Dr. Horácio Kneese de Melo of Brazil is an interesting presentation of the normal variations of augmented unipolar extremity leads. In Chapter I, he discusses the advantages of unipolar leads in general. In Chapter II, he describes Goldberger's modification of Wilson's central terminal, which he uses. He states that he found that the augmented unipolar extremity leads taken with or without the resistors are identical. In Chapter III, he reviews Wilson's description of the electrical positions of the heart, which he employs, and he describes a variation of the Einthoven triangle for use with unipolar extremity leads.

The remaining five chapters describe his observations of the aV leads in 221 normal subjects, including newborn infants and children. His observations on the T wave are especially interest-

ing. He found an upward T in Lead aV_R in several of his newborn subjects. This has not been previously noted. In the aV_L lead a downward T with a tall R occurred in only one adult. In the aV_F lead, a downward T with a tall R was common in children and adolescents.

The monograph is written in Portuguese in a simple and easy style. It is well printed and the illustrations are clear.

EMANUEL GOLDBERGER, M.D.

FISIOPATOLOGIA DELLA CIRCOLAZIONE VENOSA. By L. Condorelli, Corso, Italy, 1946, Azienda Poligrafica Editoriale, 336 pages and 83 tracings, 1200 lire.

This book is a monographic study of the venous circulation. Most of the material presented has already been published by the author and his pupils. After describing a new apparatus for continuous recording of venous pressure in man, the author applies the results of the method to the interpretation of various circulatory conditions.

While much of the present physiologic knowledge concerning venous circulation is ignored, some new conceptions are advanced. Some of these, such as that concerning venous hypertonus (so-called "active" venous hypertension), are attractive but do not seem to be substantiated by solid evidence. Bibliographic quotations are chiefly limited to French and German work of the last ten years.

The author presents a large material with undeniable skill, but the style and composition of the book are far from being clear.

A. LUISADA, M.D.

TEMPI DI CIRCOLO E VELOCITÀ DISTRETTUALE DI CORRENTE. By A. Francaviglia and A. Turchetti, Catania, 1946, Azienda Poligrafica Editoriale, 254 pages and 36 figures, price: 680 lire.

This book deals with circulation time and circulation speed with special regard to the rate of circulation in limited sections of the cardiovascular system. After a review of the different methods for measuring circulation time, the authors state the reasons for choosing sodium dehydrocholate. Using this drug, circulation rate is studied in normal subjects before and after the administration of drugs, exertion, compression of the eyeballs, apnea or forced respiration, and introduction of air in the course of therapeutic pneumothorax. It is further studied in cardiac patients before and after exertion, and in hypertensive and hypotensive patients. In a later chapter, circulation time and speed are measured in limited sections of the cardiovascular system.

While a great deal of data has been collected, some of them of interest, their evaluation is by no means easy. This is due to the failure of the author to clearly separate personal observation from the observations of others, poor distribution of the subject, and the failure to clearly summarize the results and conclusions of the study.

A. LUISADA, M.D.

A DOENÇA DE CHAGAS NA BAHIA. By Prof. Adriano de Azevedo Ponde', Bahia, 1947, Imprensa Vitoria, 126 pages and 107 figures.

Chagas' disease is South American trypanosomiasis. It differs from the African sleeping sickness in its clinical manifestations. It has an acute and a chronic form. In the chronic form, nervous system or cardiovascular symptoms predominate. Several descriptions of the cardiac aspects of Chagas' disease are found in the South American literature and a short description may be found in White's "Heart Disease." Most cases occur in Brazil, and on the basis of thirty-seven cases, this monograph presents the clinical picture which is quite different from anything cardiologists ever see in this country.

Patients acquire the disease by sleeping in dwellings infested with *Triatoma magista*, a bug which carries the *Trypanosoma cruzi* and sucks the blood of its victims at night. The *Trypanosoma* seeks with preference the myocardium where it sometimes may be found, post mortem, imbedded within the myocardial fibers.

The clinical picture which it produces is one of congestive failure which persists for months or years, proves resistant to treatment except for temporary remissions, and finally ends in death from asystole.

Of thirty-six cases of chronic Chagas' disease, thirty were between 11 and 40 years, seventeen between 21 and 30 years of age. Thus, it is a disease of young adults. The symptoms were palpitation, dyspnea, and various precordial pains of rather indefinite nature. As congestive failure developed, enlargement of the liver and dependent edema (right-sided failure) predominated, signs of left-sided failure being much less marked. Cardiac enlargement was frequent but varied greatly in degree. Valvular involvement was no part of the picture, though systolic murmurs might arise from relative mitral insufficiency.

Most extraordinary, however, were the electrocardiographic findings: this disease causes extensive damage to impulse formation, the conduction system, and the myocardium. All kinds of ectopic origins of complexes are seen both in auricles and ventricles. Auriculoventricular block is more common in this form of heart disease than in any other, eleven of the thirty-six cases of chronic Chagas' disease had complete A-V dissociation, and six others had incomplete A-V block. Another peculiarity is the frequency of right bundle branch block. Typical and persistent left bundle branch block was not seen in this series. No satisfactory explanation is given for this predominance of right ventricular pathology and failure. Another unusual feature was the changes which the electrocardiographic alterations underwent, especially in the S-T and T segments when serial tracings were taken.

Altogether, Chagas' disease of the heart, as described by this able cardiologist, presents an intriguing and interesting picture, quite novel to the more or less standardized patterns to which we have become accustomed.

Anyone who wishes to read this book will do well to orient himself by first reading a chapter in a textbook on tropical diseases such as the textbook by Bercovitz. The case reports are full and complete, occupying pages 14 to 87. Then follows an analysis of the material, a discussion which contains the essence of the subject, and finally an abstract in English which becomes a little clearer if one has first mastered the Portuguese text. The references appear to be adequate and ample.

JULIUS JENSEN, M.D.

SEMEIOLOGIA CARDIOVASCULAR. By R. Carral y de Teresa, México, 1947, Instituto Nacional de Cardiología, 500 pages and 93 figures.

This book is devoted to "Cardiovascular Semeiology." The first part deals with functional semeiology, including a study of dyspnea, cyanosis, precordial pain, and cerebral symptoms. The second part deals with hemodynamics. The mechanisms of cardiac failure, venous hypertension, serous effusions, cardiac output, circulation speed, and blood pressure are discussed, with separate chapters for hypertension and hypotension. In the third part, physical examination is described with special emphasis on auscultation. The mechanism of production of murmurs and phonocardiography is discussed in detail. The last three parts are respectively devoted to various laboratory methods, roentgenology, and electrocardiography.

The book contains a rich and well-organized collection of data which make its reading interesting and easy. The quotations from the literature are well chosen and those from the works of Mexican authors are particularly interesting and useful.

While illustrations of methods of physical examination would have increased the value of the book for beginners, the roentgenologic, stethographic, and electrocardiographic tracings are clear and, at times, particularly interesting. The main fault of the book is that it represents a compromise between the stated purpose of the author (semeiology) and the unexpressed wish of writing a book on cardiology. If the title is correct, repeated description of clinical entities, including pathology, and detailed discussion of therapeutic procedures are superfluous. In a book on cardiology, the order of the chapters should be different and the space devoted to description of symptoms and signs should be more proportionate to the total volume. Inclusion of chapters devoted to peripheral circulation would increase the value of the book. The same can be said of an index of subjects.

A. LUISADA, M.D.

CORNELL CONFERENCE ON THERAPY, VOL. II. Edited by Harry Gold, M.D., David P. Barr, M.D., McKeen Cattell, M.D., Eugene F. Du Bois, M.D., Paul A. Bunn, M.D., and Walter Modell, M.D. New York, 1947, The Macmillan Company, 354 pages, price \$3.75.

The Editorial Board for this publication has apparently fulfilled its stated purposes, namely, to explore some aspects of special interest in pharmacology and therapeutics, to analyze the evidence on controversial points of opinion and practice and break down the physiologic and pharmacologic bases of therapeutic measures, and to present these on the level of the general practitioner. These conferences assemble many practical therapeutic facts, and in spite of the disclaimer of the editors of such an objective, the book will serve as a reference source. As such it would have been more valuable if more of a bibliography were included, especially where space prevents presentation of precise techniques. Likewise, an index would be helpful.

The discussion and question method of teaching, which is so stimulating to the individual present at a conference, at times confuses a reader of such material presented in publication. This results not only from certain verbosity, but also from conflicting opinions, especially relevant to the value of new procedures or material. From the teaching standpoint it would seem wiser either to present the most authoritative discussion, or else have the moderator more forcibly discredit probably erroneous opinions.

The presence of personal bias is apparent in the dominant opinion on certain subjects, especially the Sister Kenny treatment of poliomyelitis, the inadequacy of xanthines as diuretics, and the entire subject of quinidine therapy. The opinions expressed on the use of quinidine may be popular at present, but are not uniformly accepted by many excellent cardiologists. It is most notably illustrated on the views that quinidine must not be used with, or presumably shortly after, digitalis; it should not be used in myocardial infarction, presumably 0.2 Gm., three to four times daily as prophylactic doses, because "it depresses the myocardium too much for its use"; it rarely, if ever, should be used in conversion of permanent auricular fibrillation, overlooking the increased incidence of embolic phenomena, an opinion disputed by Dr. Pardee; it is rapidly eliminated; and that after conversion of an arrhythmia, the maintenance dose is rarely used.

Certain chapters are especially excellent reviews of the subjects considered, especially "Sympathomimetic Amines," "Edema and Dehydration," and "Rheumatic Fever." The unanswered question often indicates where investigation should be pursued, and the mode of presentation illuminates, but occasionally not as well as it should, the difference between accurate clinical observation, applied experimental data, and opinion colored by various causes of personal bias. The occasional human weaknesses shown by such an excellent group so seriously at work to avoid them is a good moral lesson to the reader in guarding the formation of his own therapeutic judgments.

JOHN J. SAMPSON, M.D.

UNIPOLAR LEAD ELECTROCARDIOGRAPHY. By Emanuel Goldberger, M.D. Philadelphia, 1947, Lea & Febiger, 82 pages and 88 figures. Price \$4.00.

This monograph describes and analyzes electrocardiographic patterns primarily in terms of unipolar leads. It is pointed out that such leads provide a recording of potentials which are not significantly affected by the indifferent electrode, and therefore can be explained in terms of simple, fundamental principles. The material presented is based on a seven-year study of these leads by the author, the study having had its origin in an investigation of the Q wave by means of Wilson leads, followed by the modification of these leads to form the augmented unipolar leads of the author.

The subject is introduced by a brief discussion of the basic principles of electrocardiography. The validity of the Einthoven triangle theory is accepted on the basis of experimental data previously published by the author and by others. The various methods of taking unipolar leads are described, including both the author's method and the use of the Wilson central terminal. Many will disagree with the advisability of omitting the 5000 ohm resistances in the former. The discussion of the relationships between the standard leads and unipolar extremity leads and between ordinary precordial leads and unipolar precordial leads is entirely adequate. Following this, the major portion of the volume is devoted to the normal electrocardiogram, to the effects

of position of the heart upon the normal electrocardiogram, and to abnormal electrocardiograms, including those associated with hypertrophy of the various chambers, bundle branch block, myocardial injury, and digitalis administration. Proper stress is placed upon the value of unipolar electrocardiography in the interpretation of many cardiac conditions in which standard electrocardiographic methods are entirely inadequate, among which might be mentioned especially the value of the left leg potentials in the interpretation of the significance of a Q wave in Lead III. No attempt is made to discuss the arrhythmias, since unipolar electrocardiography contributes nothing to their diagnosis except in cases of nodal rhythm.

Throughout the volume, tremendous stress is placed upon the effect of changes in the position of the heart through rotation upon any one of its three axes, or upon a combination of these axes. The theorizing along this line is extended to a degree which will not be acceptable to most. Corresponding radiologic descriptions of all of the positional electrocardiographic patterns are omitted, "partly because much of this information is still incomplete." Nowhere in the volume is there found the caution with regard to this subject expressed by Wilson and his co-workers in this statement, "The names given to these positions are not intended to imply that the electrocardiographic position of the heart is uniquely determined by its anatomic position, either when this organ is normal or abnormal. We are not only aware, but are also certain, that a change in the one is not necessarily accompanied by a change in the other." This warning is especially indicated when there is a localized lesion of the myocardium, and yet the positional theories are carried over without apology into the subject of myocardial infarction, and the statement is made that the heart usually lies horizontally after anterior infarction and vertically after posterior infarction. It is explained that the rotation is due to factors differing from those that affect the position of the normal or hypertrophied heart, and that the abnormal contraction of the involved portion of the myocardium, together with the force of contraction of the remaining normal muscle or in some cases localized dilatations of the wall, may be responsible for the abnormal rotation. This will be extremely difficult for many to accept without the presentation of a great deal more evidence.

In the preface the statement is made that "standard leads and unipolar extremity leads are somewhat different from the other leads because they not only depend on the basic unipolar lead patterns, but they vary greatly with changes in the position of the heart." This would seem to imply that precordial leads are not influenced by changes in the position of the heart, though this is at variance with the remainder of the text and with common experience. No attempt is made at any point in the description of precordial leads to discuss or even mention the important transitional zone and the facts that are known concerning its variability in the normal. The impression is very definitely given that the entire left ventricle gives qR or qRS patterns in unipolar leads that face its epicardial surface. This is not in accord either with experimental work with direct leads in the animal or with studies of the transitional zone in the human, since the anterior surface of the left ventricle gives rise to RS patterns, and only the lateral and posterobasal portions demonstrate an initial negative deflection in the normal heart.

Because of these objections and other less important ones, such as obscure phraseology in many places, this book cannot be recommended for one who does not have a good, basic knowledge of electrocardiography. It does contain, however, much valuable information, such as the criteria for the abnormality of the Q waves.

THOMAS M. DURANT M.D.

A PRIMER OF CARDIOLOGY. By George E. Burch, M.D., F.A.C.P., and Paul Reaser, M.D. Philadelphia, 1947, Lea & Febiger, 272 pages and 203 figures. Price \$4.50.

A Primer of Cardiology is just what the authors state it to be; a primer designed for medical students and practitioners to serve as an introduction to more serious study. As such it can be recommended. For the medical student, the authors' attempts to correlate the basic sciences of physiology, physics, and physical chemistry with clinical phenomena should be very helpful. For example, the section on heart sounds is particularly good. The correlation of phonocardiographic records with other events in the heart cycle is well done and the diagrams are very instructive. The analysis of the phenomena associated with split heart sounds and gallop rhythm is particularly good. The presentation is difficult to follow, however, because the text is so abbreviated.

There are several points throughout the book with which this reviewer does not agree. For instance, it is stated that the Graham Steell murmur indicating pulmonary insufficiency is common. The authors define heart disease as any disturbance in cardiac function that disturbs the patient in any way. This I believe to be much too broad; a concept that would make the handling of the cardiac neuroses more difficult. Under heart disease due to the aging process, the authors include arteriosclerosis of the coronary arteries. The experience with our troops, in which, I am told 1,000 young men from the ages of 18 to 40 years died of cardiac infarction, casts doubt upon the concept of this disease as an aging phenomenon. The section on cardiovascular syphilis is, in the reviewer's opinion, the poorest in the book. It contains a section on acute aortitis in which dyspnea and vague substernal pain are listed as symptoms. Aortitis is a symptomless disease. In the section on diagnosis, it is stated that aortitis is easily diagnosed and that it appears clinically after only several weeks of infection. This is certainly not the prevailing opinion. The authors are also oversanguine when they state that syphilitic aortitis will respond to therapy with complete cure if early and adequate antisyphilitic therapy is administered.

These criticisms are presented in a spirit of helpfulness and in the hope that some of them may be accepted for the next edition.

There are many very good clinical sections; the critique of our knowledge of congestive heart failure, the presentation of cardiac infarction, angina pectoris, and hypertensive heart disease. It is pleasing to see that the authors use the term diastolic hypertension.

Having read the book, this reviewer is left with the feeling that it will serve a useful purpose but that it would be more enthusiastically recommended if some of the statements enumerated could be corrected.

EDWIN P. MAYNARD, JR., M. D.

CONGENITAL MALFORMATIONS OF THE HEART. By Helen B. Taussig, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine, and Director of the Children's Cardiac Clinic at the Harriet Lane Home of the Johns Hopkins Hospital, New York, N. Y., 1947, The Commonwealth Fund, 1618 pages, 46 plates in color, 177 other illustrations. Price \$10.

Contents: Foreword by Edwards A. Park, M.D.

Part One. Physiology of the Malformed Heart and Diagnostic Principles

- I. Embryology, Etiology, Basic Principles of Analysis, and Fetal Circulation
- II. Methods of Diagnosis
- III. Cyanosis

Part Two. Malformations Which Deprive the Body of an Adequate Amount of Oxygenated Blood

- IV. Defective Development of the Right Ventricle and Tricuspid Atresia
- V. The Tetralogy of Fallot
- VI. Pulmonary Stenosis or Atresia and Extreme Dextroposition of the Aorta
- VII. Pure Pulmonary Stenosis
- VIII. Aortic Atresia and Marked Hypoplasia of the Aortic Orifice
- IX. Absence of the Aortic Arch
- X. Complete Transposition of the Great Vessels and the Common Associated Anomalies
- XI. Truncus Arteriosus
- XII. A Single Ventricle and a Rudimentary Outlet Chamber
- XIII. Anomalies of the Venous Return
- XIV. The Anomalous Origin of the Left Coronary Artery From the Pulmonary Artery

Part Three. Malformations Which Permit the Body to Receive an Oxygen Supply Sufficient for the Growth of the Individual

- XV. Persistent Patency of the Ductus Arteriosus
- XVI. Defects in the Auricular Septum
- XVII. Defects in the Ventricular Septum

- XVIII. The Eisenmenger Complex
- XIX. Aneurysm in the Sinus of Valsalva With Rupture Into the Right Ventricle
- XX. Anomalies of the Aortic Valve and of the Ascending Aorta
- XXI. Anomalies of the Aortic Arch
- XXII. Coarctation of the Aorta
- XXIII. Dextrocardia With or Without Situs Inversus
- XXIV. Ebstein's Disease
- XXV. Complete Heart Block and Other Cardiac Arrhythmias

Part Four. Therapeutic Measures

- XXVI. General Medical Care
- XXVII. Medical Aspects of the Surgical Correction of Congenital Pulmonary Stenosis or Atresia

Correlation of the Salient Features Aiding in Diagnosis

Index

Helen Taussig's new book on congenital heart disease is a milestone in both the development and the distribution of our knowledge about the heart. She has done important pioneering herself and has presented in some detail these contributions of her own. Also, she has covered in a clear and concise form a good deal that is known about congenital heart disease that has come from other sources. However, one would have liked to have had included in this book more of the new work that has been going on in the physiologic study of congenital defects of the heart; in particular, by cardiac catheterization. Events move so rapidly that there has come new information within the last year or so that was not included in this book; for example, the current availability of the determination of pulmonary blood pressure by cardiac catheterization, doing away with our guesswork of former days and with the need of waiting until actual operation before measuring the pulmonary blood pressure. There is also inadequate recognition of the increasing success of penicillin therapy in the treatment of subacute bacterial endocarditis as a complication and the displacement of sulfonamide therapy by penicillin. Similarly, one would like to see in future editions x-ray pictures of Diodrast injections to reinforce the excellent diagrams that appear throughout the book.

Some readers may complain of the lack of long discussions about embryology, but this book is avowedly a clinical treatise and contains, in the opinion of the reviewer, an adequate amount of reference to the fetal development of the heart itself.

The author's pioneer contributions have been largely in the field of the cyanotic types of congenital heart disease and are particularly presented in Chapter IV (Defective Development of the Right Ventricle and Tricuspid Atresia), Chapter V (The Tetralogy of Fallot, in the remarkable surgical treatment of which Taussig's name is forever emblazoned along with that of Blalock), Chapter X (Complete Transposition of the Great Vessels and the Common Associated Anomalies), and Chapter XIII (Anomalies of the Venous Return). Also in Chapter XXI (Anomalies of the Aortic Arch) in Part Three, which concerns the noncyanotic types of heart disease, Taussig has presented an unusually helpful discussion based on a good deal of her own studies of congenital heart disease.

The reviewer on reading through this volume has noted down in particular several statements that deserve more emphasis than has sometimes been accorded. A few examples follow herewith.

On page 15 she states: "All the present experimental evidence indicates that although anatomical closure of the ductus arteriosus may not be completed for two months, functional closure of the ductus arteriosus occurs shortly after birth."

On page 18, there is a sentence which is important for the internist to remember, namely that "The infant's heart is larger in proportion to the chest than is that of the adult" and on page 24 there is the observation that "in the infant the chest is wider than it is long, in the child approximately as long as it is wide, and in the adult longer than it is wide" and that "in infancy the difference in pressure between the two circulations is slight; with variations in the systemic and pulmonary pressure, murmurs come and go. Therefore, too great emphasis should not be placed on murmurs."

On page 20 we find "A reduplication of the second sound is clear evidence of the existence of both great vessels" and on page 22 "cyanosis always precedes clubbing of the extremities; indeed clubbing of the extremities, although a characteristic finding in older patients, is seldom seen in early infancy." In referring to râles in the lungs due to pulmonary congestion, not infection, the author writes that since most malformations which cause persistent cyanosis are associated with marked diminution in the flow of blood to the lungs, "therefore, cyanosis accompanied by râles indicates a malformation which permits adequate circulation to the lungs."

On page 48 we find "The P waves give some information concerning the size of the auricles. Abnormally high pointed P waves occur with great enlargement of the right auricle. Notching and prolongation of the P waves are seen with enlargement of the left auricle."

On page 54 there is the statement "Most infants in whom cyanosis is due primarily to a large venous-arterial shunt and to the failure of the blood to reach the lungs for oxygenation die at an early age. For this reason secondary changes in the lungs become of increasing importance in the older age groups. These pulmonary factors become so pronounced in adults that many internists believe that they are of far greater importance than is the reduction in the pulmonary circulation," especially in the case of the Eisenmenger complex in which there is evidence of pulmonary or endarterial change.

One could continue to quote many other interesting and instructive passages through the book which it would be well for both the internist and cardiologist, *per se*, to read carefully. Such passages appear right to the end of the whole book. Near the end, for example, on page 550 there is the following interesting advice: "Broadly speaking, if the cardiothoracic ratio is 55 per cent or under, a child with a congenital malformation of the heart does not need digitalis. With a cardiothoracic ratio of 55 to 64 per cent he may or may not need digitalis; with a cardiothoracic ratio of 65 per cent or over, compensation can seldom be maintained without the aid of digitalis."

The reviewer would like to emphasize particularly the excellence of the plates of which there are forty-six in color; with their legends they would make a very good atlas, *per se*. Plate 35, however, is a bit unsatisfactory and could be improved to make it clearer. The other illustrations also are good; they include line drawings, teleroentgenograms, electrocardiograms, and a few other subjects. At the end of the book there is a tabular appendix, a useful summary of the clinical findings. There is also a very adequate index of thirty-six pages.

The author has emphasized the preponderant importance of x-ray study in the diagnosis of the individual congenital defects, but much experience and skill is needed to follow that lead. The left anterior oblique position, both for roentgenograms and fluoroscopy, is constantly referred to as of the greatest value in determining the relative sizes of the heart chambers. Doubtless there are difficulties involved, as for example, when the heart is so large that it may be impossible to tell whether both chambers are enlarged or whether one or the other is so much enlarged that it displaces the other anteriorly or posteriorly. The value of electrocardiography is perhaps somewhat greater than considered in this book, for, on occasion, as in the case of tricuspid atresia, it is possibly the most important or most rapid clue to the diagnosis.

The more adverse criticisms of the reviewer concern, in the first place, the incompleteness of the book with respect to such a subject as cardiac catheterization which, he thinks, might well be included in the next edition, and second, considerable repetition, particularly with reference to chapter summaries. A good many pages are taken up with chapter summaries, the time for the reading of which could be better devoted to a rereading of the chapter itself; for example, Chapter XXVII with 19 pages has three devoted entirely to the summary. Since the plates also give quite satisfactory summaries of each condition, the chapter summaries might well be omitted with the saving of many pages.

There are surprisingly few errors of spelling or construction and also very few omissions of important matter. A comment might have been well added about the possible strain on the heart (to be watched with interest in the future) which may result from the Blalock-Taussig operation in which the shunt, somewhat like that of a ductus arteriosus, is artificially produced.

In conclusion, this book by an expert specialist can be highly recommended to serve both as a textbook to read, *per se*, and for reference after that for cardiologists, general internists, general practitioners, and medical students alike.

P. D. WHITE, M.D.

American Heart Association, Inc.

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Telephone Plaza 7-2045

NEW HEADQUARTERS FOR AMERICAN HEART ASSOCIATION

The American Heart Association has moved its offices from 1790 Broadway to 1775 Broadway, New York 19, N. Y. The new telephone number is Plaza 7-2045.

SCIENTIFIC COUNCIL

A list of more than 700 names to comprise the Founder's Group of the Scientific Council has been approved by the Board of Directors. Membership in the Council is granted on the basis of training and scientific contributions to the field of cardiovascular disease. It is a requirement that all members of the Scientific Council shall be or become members of the Association.

The first meeting of the Scientific Council will be held in Chicago in June, 1948, at the time of the Annual Scientific Sessions.

PROCEEDINGS FOR THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

These proceedings appeared in the May issue of the AMERICAN HEART JOURNAL. In order that they appear at the earliest possible moment, an explanation of their inclusion in the JOURNAL had to be omitted. The American Heart Association, the editors, and the publishers now wish to express their appreciation to the American Society for the Study of Arteriosclerosis for the privilege of presenting these proceedings.

THE GEORGE BROWN MEMORIAL LECTURE

In the announced program of the Twenty-first Scientific Session of the American Heart Association, it was stated that the George Brown Memorial Lecture would be given by Dr. Edgar V. Allen. Unfortunately, Dr. Allen will be unable to give the lecture because of illness. Dr. Irvine H. Page of Cleveland, Ohio, has consented to take Dr. Allen's place. The title of Dr. Page's lecture is "On the Nature and Treatment of Shock."

FINANCE COMMITTEE

Formation of a Finance Committee consisting of Mr. Alfred C. Howell, Bethel, Conn.; Mr. Robert L. Mehornay, Kansas City, Mo.; Mr. S. DeWitt Clough, Chicago, Ill.; Mr. Emerson Foote, New York, N. Y.; and Mr. Samuel Harrell, Indianapolis, Ind., Treasurer, has been approved by the Board of Directors. Mr. Howell will serve as Chairman of the Committee.

CONGRESSIONAL HEARINGS ON HEART DISEASE LEGISLATION

Representatives of the American Heart Association, including Arlie R. Barnes, M.D., President; Charles A. R. Connor, M.D., Medical Director; David D. Rutstein, M.D.; and T. Duckett Jones, M.D., presented statements at the hearings on Bill S-2215, a bill to provide for research and control relating to diseases of the heart and circulation, before the Sub-Committee on Health of the Committee on Labor and Public Welfare of the United States Senate, on April 8th.

The Bill, which provides for the formation of a National Heart Institute in the National Institute of Health within the United States Public Health Service, received the endorsement

of the Association's representatives with several modifications. These mainly concerned the functions of the National Heart Council, which would be specifically empowered to provide the necessary guidance to the Surgeon General of the United States Public Health Service in carrying out the provisions of the Bill.

It was recommended that the powers of the National Heart Council be made similar to those of the National Advisory Cancer Committee, and that it be authorized to (1) review research projects or programs and recommend to the Surgeon General such projects it believed to show promise of making valuable contributions to human knowledge; (2) review applications for grants-in-aid of research and demonstration projects and certify to the Surgeon General its approval of such projects; (3) review applications for grants-in-aid for training and instruction and certify to the Surgeon General its approval of such applications; and (4) advise, consult with, and make recommendations to the Surgeon General with respect to carrying out the provisions of this Act.

It was also recommended that six of the twelve Council Members be selected from leading medical or scientific authorities who are outstanding in the study, diagnosis, and treatment of cardiovascular diseases.

The testimony presented by Doctors Barnes, Connor, Rutstein, and Jones was in accord with the action taken by the Executive Committee of the Association on May 5, 1947, in approving many of the provisions of the Bill (HR 3762) presented by Representative K. Javits of New York.

The Javits Bill, as well as other suggested legislation relating to research in diseases of the heart and blood vessels, received public hearings before the Committee of Interstate and Foreign Commerce of the House of Representatives on May 5 and 6, 1948. Action taken on Senate and House bills will be reported in future issues of the JOURNAL.

PAUL WHITEMAN CONTEST

Public contributions made to the American Heart Association through the American Council on Rheumatic Fever in the Paul Whiteman "Memory Tune Contest" have amounted to approximately \$25,250. The contest, which was broadcast over the American Broadcasting Company network, ran for four weeks beginning March 1. More than 119,000 letters were entered in the contest.

RESEARCH GRANTS

The Life Insurance Medical Research Fund has announced the award of forty-three grants-in-aid of research in the field of cardiovascular disease and fourteen postgraduate fellowships for research. The total sum granted for research programs is \$484,790. The amount awarded with fellowships is \$52,600. Postgraduate fellowship stipends vary from \$2,500 to \$4,000.

These awards bring the total sum made available for aid to medical research by the Life Insurance Medical Research Fund since its organization in December, 1945, to approximately \$1,800,000.

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For the Study of the
CIRCULATION



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